SYNTHESIS OF PIPERIDINE DERIVATIVES HAVING POTENTIAL THERAPEUTIC PROPERTIES

Thesis submitted

for

the fulfilment of the

Degree of

Doctor of Philosophy

by

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IN THE NAME OF ALLAH
THE MOST COMPASSIONATE
THE MOST MERCIFUL

Dedicated to

My Mother

ACKNOWLEDGEMENT

I bow my head before Almighty Allah by whose grace I have successfully achieved what I strived for.

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SUMMARY

Piperidine is among the most important heterocyclic compounds which exhibits most of therapeutic activities due to it's conformationally flexible nature. Molecular modifications of pethidine and morphine like compounds led to the syntheses of new opiates having agonistic as well as antagonistic activities. In many families of opiate narcotic analgesics, small changes in chemical structures have shown to modify the extent to which an analogue exhibits agonist and antagonist activity.

During the course of present work three series of substituted phenacyl and one series of 1-adamantyl methyl ketone, derivatives of 4-hydroxypiperidine, 4-hydroxy-4-phenylpiperidine, 4-acetyl-4-phenylpiperidine and 2-piperidineethanol were synthesized. The resulting derivatives were screened for analgesic activity by chemical and thermal method. Most of the compounds exhibited analgesic activity when evaluated by chemical method whereas all the compounds proved to be inactive by thermal method.

Halogen substituted phenacyl derivatives among all the series displayed maximum activity in acetic acid induced writhing assay as compared to other substituted derivatives.

Eight derivatives which exhibited maximum percent inhibition of acetic acid induced writhing among their respective series, were selected for studying their effects on brain monoamine levels in male albino mice.

Phenacyl derivatives of 4-hydroxypiperidine, 4-hydroxy-4-phenylpiperidine and 4-acetyl-4-phenylpiperidine were also evaluated for their effects on mean arterial blood pressure in normotensive anaesthetized rats and spontaneous contractions of rabbit jejunum. Most of the compounds exhibited hypotensive and hypertensive effects at the dose range of 3-10 mg/kg body weight.

Compound **XVII**, **XXXI** and **XXXII** [1-(2',4'-dimethoxyphenacyl)-4-hydroxy-4-phenylpiperidinium bromide, 1-(4'-bromophenacyl)-4-acetyl-4-phenyl-piperidinium bromide and 1-(4'-chlorophenacyl)-4-acetyl-4-phenylpiperidinium bromide] were found to be the most potent antihypertensive agents as they caused 84, 88 and 83% fall in blood pressure respectively at the dose of 3 mg/kg and relaxant effects on isolated jejunum at 0.3 mg/kg dose.

Spectroscopic techniques such as ^{1}H-NMR, EIMS, UV and IR were utilized for the characterization and structure confirmation of the compounds.

INTRODUCTION

The analgesic properties of opium have been recognized since the dawn of history and it is not surprising that man, whose life has been dominated by misery and pain, seized upon opium as a God given gift sent to relieve the suffering of his mind and body. The most important constituent of opium is morphine, a drug which has been responsible for easing the pain of millions who would otherwise have suffered in agony.

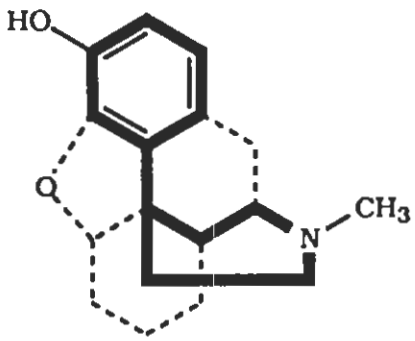
Though morphine is an extremely effective analgesic, it has an associated series of side effects that limit its legitimate use. The most prominent among these is, of course, its tendency to cause physical addiction. A significant amount of work has thus been devoted to the synthesis of analogues with a view to modify the pharmacological spectrum and, in particular, avoiding its addiction potentials.

Extensive molecular dissection of morphine molecule over the past several decades led to a host of molecules which showed narcotic analgesic activity even though they possessed but faint

suggestions of the structural features present in morphine itself.

Examination of the morphine molecule (**1**) reveals the presence of a 4-phenylpiperidine fragment within the molecule. It was presumably this line of reasoning that led to yet another extensive series of synthetic analgesics. The greater diversity of structural types that have exhibited analgesic activity has led medicinal chemists to seek the thread common to these various molecules. The so called "morphine rule" represents one formulation of elements shared by the large majority of analgesics.

Briefly, activity seems to require an aromatic ring (a) attached to a quaternary centre (b) and a tertiary nitrogen (c) removed at a distance of two carbon atoms from (a). Like most such generalizations, this rule has its exceptions; fentanyl (**3**), for example, does not fit the rule very well.



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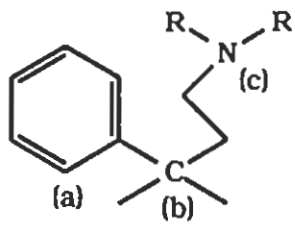

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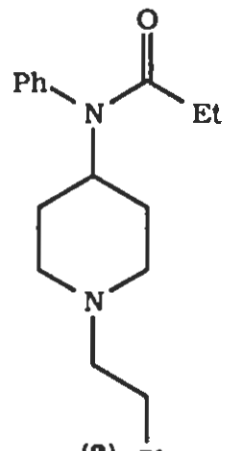
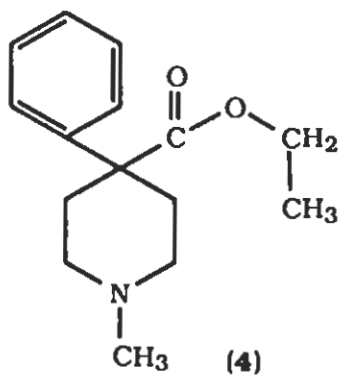


(3)

From the brief account of synthetic fragments it is apparent that morphine has been dissected in many possible ways in the hope that efficacious compounds would result. Despite the thoroughness and comprehensive characters of these researches, efforts to find new analgesic compounds preferable to morphine met with little success until Eisleb and Schaumann (1939) prepared a large number of piperidine derivatives with the intention of testing them for spasmolytic activity; atropine was regarded as the parent structure. Fortunately, several of these compounds were observed to exhibit marked analgesic properties in addition to atropine like action.

A post-facto inspection of their molecular structure (**5**) only then brought about the realization that they constituted a

fragment of the morphine molecule, namely 4-phenylpiperidine moiety, C-4 being quaternary. The two syntheses used by Eisleb in the preparation of this series permitted a wide variation of structure without profoundly changing the synthetic approach. Approximately 40 piperidine derivatives containing, in the 4-position, an aromatic ring and a number of unsaturated functions (keto, nitrile and ester) were tested, and those with the most favourable therapeutic index were chosen for clinical trials.



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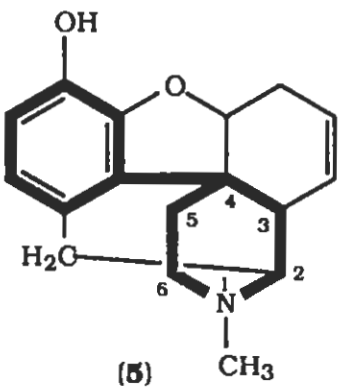

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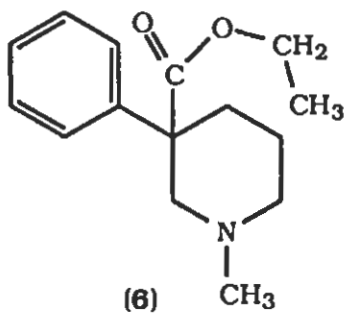


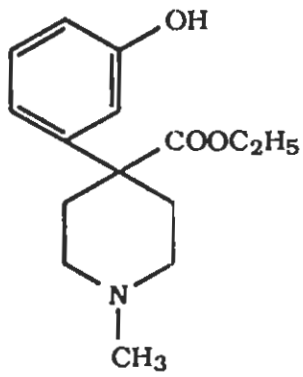
(6)

The most important substance to emerge from this happy combination of luck and a pharmacologist's acumen was 1-methyl-4-carbethoxy-4-phenylpiperidine (Meperidine, **4**), with about 1/8 the potency of morphine in man (Lasagna and Beecher, 1954).

Beta pethidine (**6**) (Bergel *et al.*, 1944), a structural isomer of meperidine with the phenyl and carbethoxy groups in the 3-position, has been studied in the laboratory animals (Macdonald *et al.*, 1956) and man (Glazebrook and Branwood, 1945). It has a low toxicity but is a less potent, shorter acting analgesic than meperidine.

Earlier work on the structural modification of pethidine has been reviewed (Braenden *et al.*, 1955) and advances upto 1957 have been surveyed by Beckett and Casy (1957). The most potent analgesic of the meperidine series, ketobemidone (**8**) (Avison and Morrison 1950, Kagi and Miescher, 1949) resulted from a double modification of the molecule. The first consists in the introduction of a hydroxyl group into the *meta* position of the benzene nucleus and produces bemidone (**7**) (Macdonald *et al.*, 1956) with activity comparable to the parent meperidine. In the second change carbethoxy group of bemidone is replaced by propionyl to give ketobemidone, which is 20 times more potent than meperidine. Another interesting modification of meperidine has been presented in 4-(6-hydroxy-3-methylphenyl)-1-isonipecotic acid lactone (**9**).

This internal ester showed considerable activity in man (Spielman, 1950).



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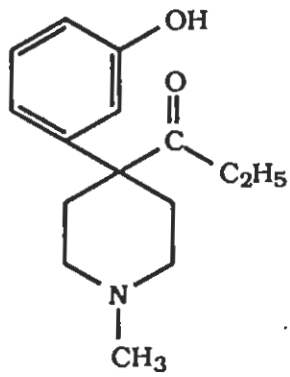

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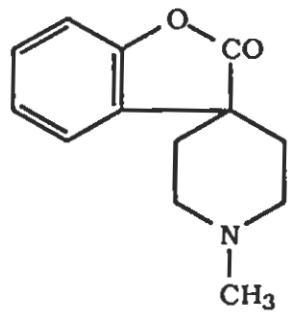
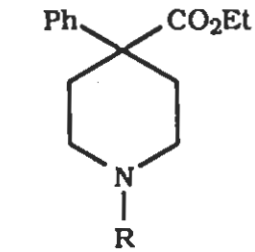


(9)

The structural variation most thoroughly investigated is the replacement of *N*-methyl by other groups, notably phenyl alkyl, brought about in most cases by alkylation of norpethidine with the appropriate alkyl or alkyl halide. These studies probably stem from the observation made by Perrine and Eddy (1956) that *N*-phenethyl norpethidine is twice as active as pethidine in mice. Elpern, Gardner and Grumbach (1957) examined the effect on activity in rats of lengthening the alkyl chain between the ring nitrogen atom and the aryl group, of chain branching and of the influence of substituents in the phenyl ring.

In the study of *N*-substituents mentioned above (Elpern *et al.*, 1957), activity was found to increase still further when the

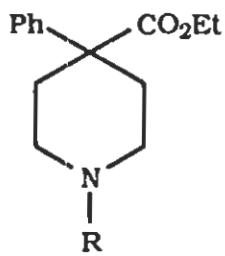
three carbon chain contained a double bond (N-cinnamyl analogue, **10**) but this is lost when a triple bond is included.



R = PhCH = $CHCH_2$

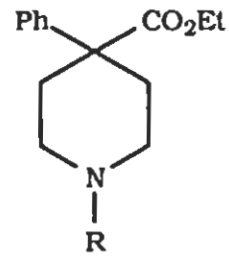
(10)

A further series of compounds (**11**) was prepared (Elpern *et al.*, 1959) in which an imino group was placed between the aryl and alkyl portion of the aralkyl substituents; several of these compounds showed very high activities. Another paper(Elpern *et al.*, 1960) relates to norpethidine substituted with long chain alkyl groups (**12**); these compounds were highly active in mice, and alpha branching did not markedly depress activity.



R = $PhNH(CH_2)_2$

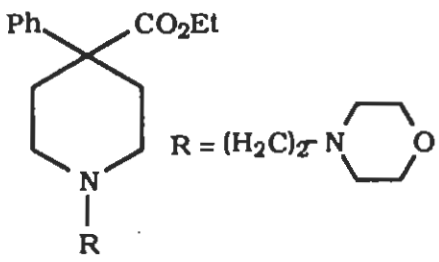
(11)



a) R = C_6H_{13} e) R = $C_{10}H_{21}$
b) R = C_7H_{15} f) R = BuCHMe
c) R = C_8H_{17} g) R = BuCHEt
d) R = C_9H_{19}

(12)

An examination of *N*-substituted norpethidines bearing alkyl groups terminated by various oxygen functions(Frearson *et al.*, 1958 and 1960) derives from the observation that while 2-morpholinoethylnorpethidine (**13**) and it's sulphur analogues possess marked analgesic potency, replacement of oxygen (or sulphur) in the heterocyclic residue by carbon or nitrogen gives inactive compounds. This indicates that the presence of an oxygen or sulphur atom at some distance from the basic centre is desirable in this series of pethidine analogues (Anderson *et al.*, Millar and Stephenson, 1956). The compounds prepared have the general formula (**14**). In the alkyl series, the 2-ethoxyethyl and 4-ethoxybutyl compounds are the most potent, being 5 and 10 times as active as pethidine respectively (Blair and Stephenson, 1960). The phenyl and benzyl analogues (**14a,b**) are about 7 times as active as pethidine. Substitution in the aromatic ring reduces potency and so does replacement of the alkoxy or aryloxy oxygen by sulphur. Inclusion of an additional ether group in the *N*-alkyl chain gives highly active compounds, *N*-2-(tetrahydrofurfuryloxy) ethylnorpethidine (furethidine, **14c**) being reported as 25 times as active as pethidine.



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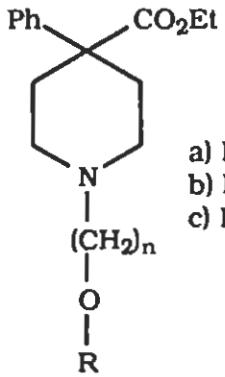
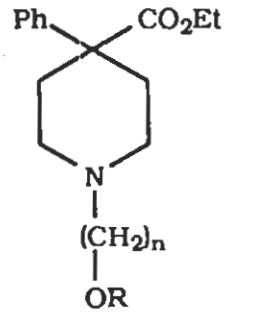


a) R = phenyl
b) R = benzyl
c) R = tetrahydro-2-furyl CH_2, n = 2

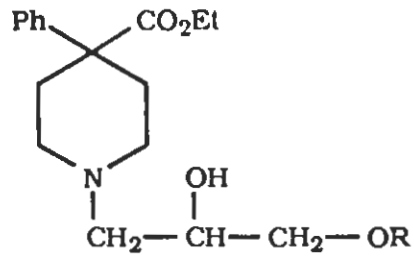
(14)

A similar series, including some previously known compounds was prepared by Morren and Strubbe (1957), who confirmed that enhanced activity may be achieved by inclusion of simple ether substituents in the *N*-alkyl chain. The 2-(2-hydroxyethoxy)ethyl compound (**15**) is particularly potent (Merlevede and Levis, 1958) and available commercially in Belgium under the trade name etoxiridine. Yet another series was prepared by condensing 3- aryloxypropane-1,2-epoxides with norpethidine to give *N*-(3-aryloxy-2-hydroxypropyl)norpethidine (Boggiano *et al.*, 1959, **16**). The unique feature of this series is the 2-hydroxy group, which is shown to be important for analgesic action since the propanediol derivative (**16a**) is reported to be twice as active as the 3-phenoxypropyl analogue (Bianchi and David, 1960).



R = CH_2CH_2OH
n = 2

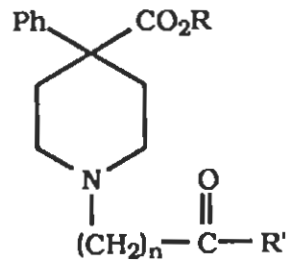
(15)



a) R = Ph

(16)

A series of aralkylnorpethidine has been studied in which the alkyl chain is separated from the aryl residue by a carbonyl group (Janssen *et al.*, 1959a and 1960b). The compounds (**17**) are Mannich bases and highest activity was found in 2-propiophenone compound (R 951, **17a**), which is 60 and 200 times more active than pethidine in mice and rats respectively (Janssen *et al.*, 1959a). Increase of the alkyl chain length to three carbon atoms is supposed to reduce potency and substitution in the aryl group (R') has also similar effect although the decrease is small with the *m*-fluoro derivative.

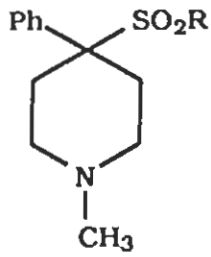


a) R = Et
R' = Ph
n = 2

(17)

The effect of varying the ester group (R) has also been studied; activity increases from methyl to ethyl, and then decreases rapidly with increase in chain length to butyl (Janssen *et al.*, 1959c). The secondary alcohol derived by the reduction of the ketone, is somewhat more active than it's precursor, but it's acetyl derivative is less active than the ketone. In the butyrophenone series, the ketone and derived alcohol have similar activities (Janssen and Eddy, 1960a).

A group of Swiss workers (Buchi *et al.*, 1952 and 1953) reported the preparation of a series of 4-alkylsulphone pethidine analogues (**18**) and found a number of these to be as effective as pethidine in mice in test for analgesia. Some non-basic derivatives were also reported to have activities of the same order as that of pethidine.



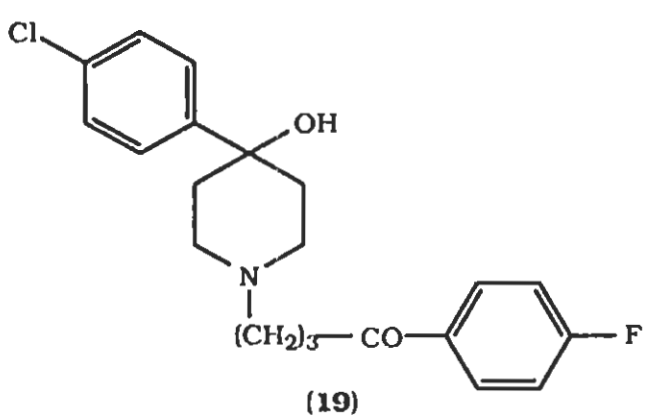
(18)

The original observation (Jensen *et al.*, 1943) that replacement of the ethoxycarbonyl group of pethidine by a propionoxy group is attended by an increase in potency has since been confirmed in numerous cases. Such a change usually produces a 20- fold increase in activity, regardless of the nature of the N substituent (Janssen and Eddy, 1960a). In most cases, propionoxy esters are more active than acetoxy esters although Beckett *et al.*, (1959) found the reverse to be true with esters of 1-phenethyl-4-aryl-4-piperidinols.

The results of replacement of *N*-methyl by *N*-aralkyl groups in esters of 4-aryl-4-piperidinols are qualitatively similar to those obtained in pethidine series. A large number of esters of 4-aryl-1-phenethyl-4-piperidinol have been prepared and each compound was found to be more potent than the corresponding *N*-methyl analogue (Beckett *et al.*, 1959). Some 4-aryl and 4-aralkylpiperidinols, in contrast to their esters,

are CNS depressants of the tranquilizing type (e.g. haloperidol

19, Janssen *et al.*, 1959d) rather than analgesics. 4-Acetoxy-1-isopropyl-4-phenylpiperidine has significant analgesic activity



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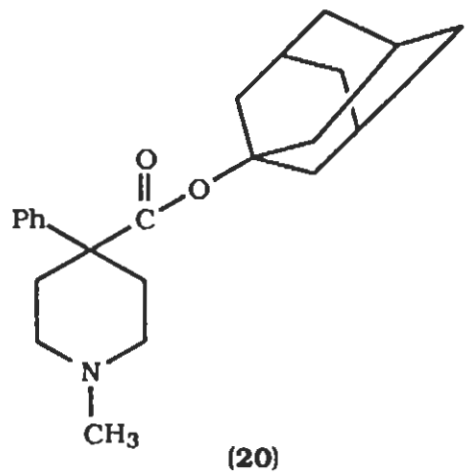


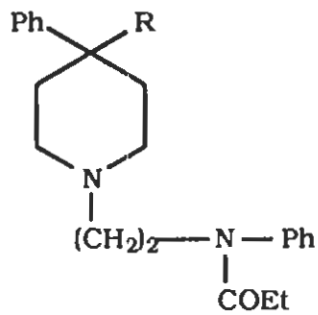
(20)

in mice but *N*-dimethylamino analogue (a hydrazine derivative) is much weaker, inspite of the two *N*-substituents being of similar size (Beckett and Greenhill, 1961). Incorporation of the adamantyl moiety into the ester function of pethidine, giving (**20**) is claimed to be advantageous both in terms of potency and duration of action (Voldeng *et al.*, 1968).

Normally *t*-alcohols corresponding to reversed ester analgesics are inactive (Beckett and Casy, 1965). The free alcohol (**21a**) however, isolated during attempts to prepare the O-propionyl ester, is highly potent in rats and it's activity is in fact reduced on esterification (**21b**). (Carabateas *et al.*, 1963). *N*-

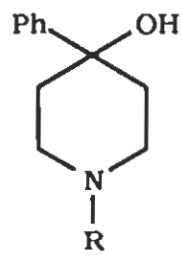
acetyl, *N*-butanoyl and 3 methyl analogues of (**21a**) and the 4-

active. Even higher potency levels are reached in branched chain congeners (**22a-b**) the activity of former being noteworthy (Fancher *et al.*, 1964). Analogues of **22** with OH replaced by hydrogen are less active, but still superior in potency to morphine.



a) R = OH
b) R = OCOEt
c) R = H

(21)

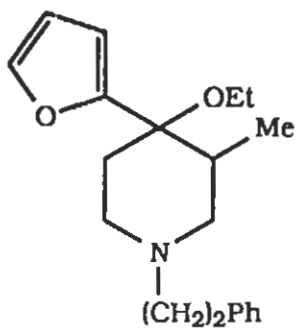


a) R = $CH_2CHMeN(COEt)Ph$
b) R = $CHMeCH_2N(COEt)Ph$

(22)

The morphine-like potency (Casy *et al.*, 1961) of the 4-(2-furyl) ether (**23**) raises the question of the general acceptability or otherwise of a 4-alkoxy group as the C-4 oxygen function in the 4-phenylpiperidine analgesics. Comparison of the relative activities of several 4-phenyl and 4-(2-furyl) pairs such as **24** shows that the heteroaryl group is not essential feature of active 4- alkoxy-4-(2-furyl) piperidines.

Hence, 4-alkoxy groups fulfill structural requirements for activity in 4-phenylpiperidines although not so effectively as 4-acyloxy functions (Casy and Armstrong, 1965).



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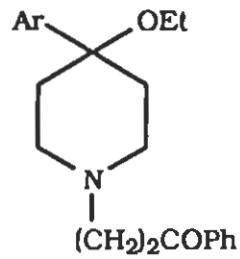
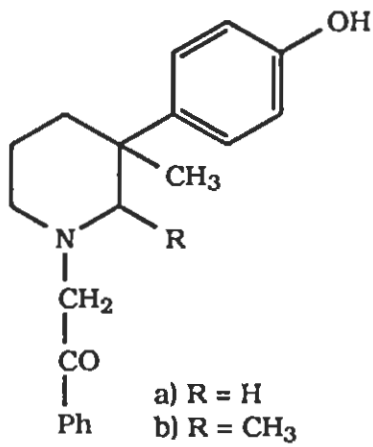


a) Ar = Ph
b) Ar = 2-furyl

(24)

Some 3-phenylpiperidine derivatives with significant analgesic activities have been reported (Kugita *et al.*, 1963 and 1965). The most active members, for example, **25**, have *N*-phenacyl or *N*-phenethyl substituents and their action is antagonized by *N*-allyl congeners; the latter also antagonize morphine, a result in contrast with the properties of *N*-allyl analogues of pethidine and it's reversed esters (Casy *et al.*, 1968). The derivatives of 3-carbethoxy-3-phenylpyrrolidine and piperidine lack both agonist and antagonist activities (Jacoby *et al.*, 1974).

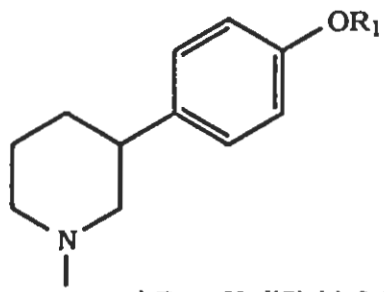


(25)

It is since two decades that much interest has been focused on the physiology and pharmacology of the dopamine (DA) auto receptor agonists, for example, apomorphine, have shown to act preferentially on the auto receptors thereby reducing nerve impulse flow, transmitter synthesis rate, and release in the CNS (Skirboll *et al.*, 1979). Functionally, stimulation of DA auto receptors results in, among other things, a decrease in locomotor activity and exploratory behaviour (Strombom, 1975). It has been suggested that compounds with selective DA-auto receptor stimulating activity may be of therapeutic value (Carlsson, 1977 and Roth, 1979).

Thirty compounds related to the selective dopamine auto receptor agonists 3-(3-hydroxyphenyl) *N*-n-propylpiperidine (3-ppp, **26**) have been synthesized and tested for central

dopamine-auto receptor stimulating activity (Hacksell *et al.*, 1981). The 3-(3-hydroxyphenyl)piperidine moiety seems to be indispensable for high potency and selectivity. Introduction of an additional hydroxyl group into the 4-position of the aromatic ring gives a compound with dopaminergic activity but lacking selectivity for auto receptors. Another paper (Wikstrom *et al.*, 1984) described the synthesis and pharmacological evaluation of enantiomeric pairs of 3-(3-hydroxyphenyl) *N*-n-propylpiperidine (**26**) in order to examine their ability to interact with central dopamine(DA) receptors, particularly DA auto receptors. In the total series, **26a** seemed to be the most interesting compound both from theoretical and therapeutical point of view and has been selected for extended pharmacological studies as a potential antipsychotic drug.

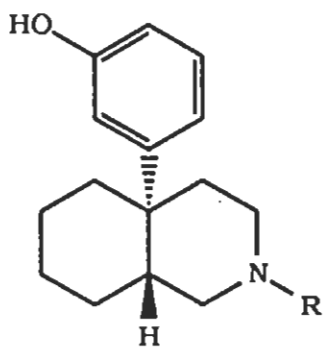


a) R_1 = H, [(S)-(-)-3-PPP]
R_2 = n-C_3H_7

26 (3-PPP)

In 3-(3-hydroxyphenyl)piperidine, theoretical studies on 2-methyl analogues, which show diminished μ-receptor affinity

and analgesic activity, have demonstrated stabilization of the equatorial phenyl conformer (Lawson *et al.*, 1988). Several constrained 3-alkyl-3-(3-hydroxyphenyl)piperidines have proved to be pharmacologically interesting: a recemic *N*-phenethyl *trans*-4a-aryldecahydroisoquinoline (**27**) has 3-10 times the potency of morphine and high μ-affinity, while the



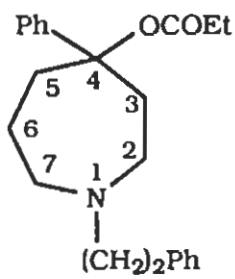
a) R = $(CH_2)_2Ph$
b) R = $CH_2OC_3H_5$

(27)

4a R, 8a R-N-cyclopropylmethyl has a mixed agonist/antagonist profile similar to pentazocine, with both μ and *k*-receptor affinity (Zimmerman *et al.*, 1988).

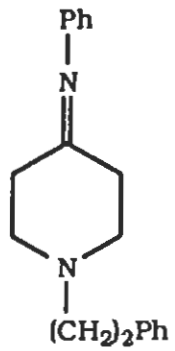
A study of ring contraction and expansion upon activity in reversed esters of pethidine together with other data show that analgesic properties are retained (although in reduced degree) in 7-membered ring of active piperidine derivatives but are absent or weak in 5-membered congeners (Casy *et al.*,

1965 and Saify, 1971). The azacycloheptane (**28**), the most active non-piperidine derivative of the reversed ester series, was a typical morphine-like analgesic, produced Straub tails and was antagonized by nalorphine, and tolerance developed towards its effects in mice.

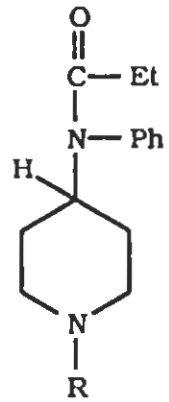


(28)

Reduction of Schiff base (**29**) formed between 1-phenethyl-4-piperidone and aniline, and acylation of the resultant dibase gives the highly potent analgesic (Janssen, 1964), fentanyl (**30a**). The *N*-methyl analogue of fentanyl (**30b**) has a radically lower potency than the parent (Casy, 1969). Riley *et al.*, (1973) first reported 3-methyl fentanyl (**31**), prepared from a 4-anilinopyridine, which proved to be 10 times more effective than fentanyl itself in rats by the tail-flick assay. Cyclic analogues of fentanyl in which the *N*-acyl group is joined to *N*-phenyl (Klein *et al.*, 1975), and *N*-phenyl linked to C-3 of the piperidine ring (Berger *et al.*, 1977), were both devoid of analgesic properties.

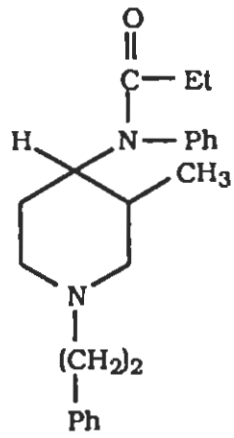


(29)



a) R = $(CH_2)_2Ph$
b) R = Me
c) R = H

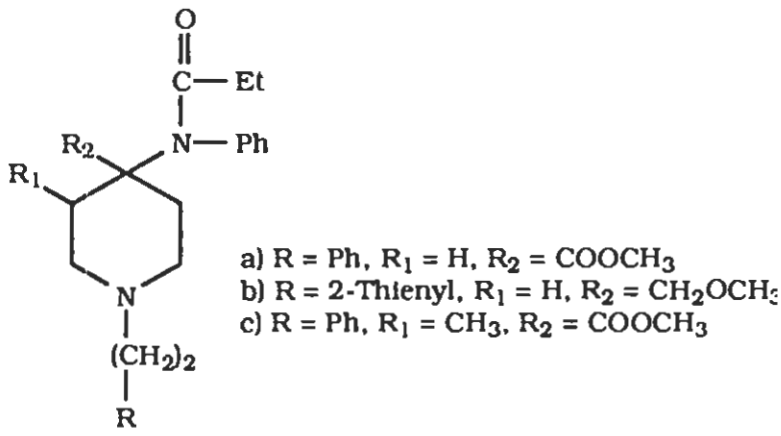
(30)



(31)

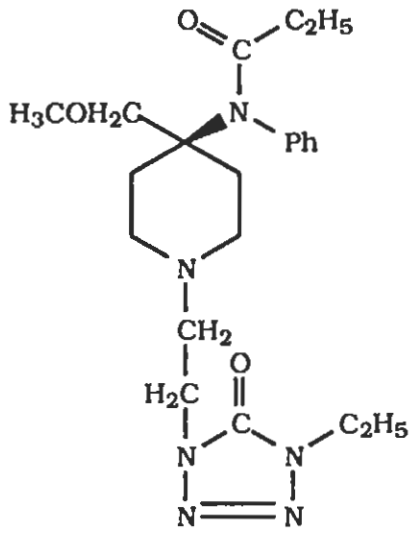
In depth investigation of the structure activity-relationship in the fentanyl meperidine series revealed that additional substitution of the amide nitrogen-bearing center resulted in still further enhancement of analgesic potency. Chemical modification of the fentanyl structure at the C-4 position of the piperidine ring proved to be successful approach (Van Daele *et al.*, 1976). Thus introduction of a carbomethoxy group gave carfentanil (**32a**), whereas addition of a methoxy methylene group coupled with isosteric replacement of the phenyl ring of the phenethyl substituent by a thienyl ring led to sufentanil (**32b**). Both carfentanil and sufentanil are very potent and long-acting analgesics. Stereospecific introduction of a methyl group at C-3 position of the piperidine moiety of the

carfentanil molecule resulted in extremely potent and long acting compound lofentanil (**32c**).



(32)

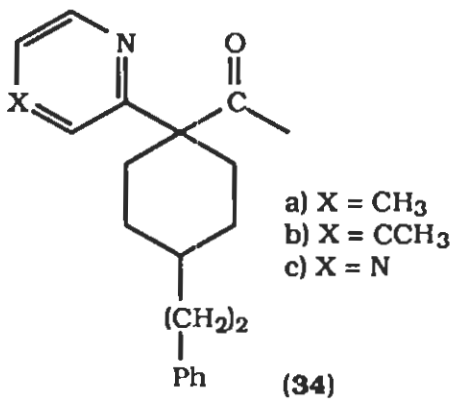
Janssen *et al.*, (1986) synthesized a series of *N*-1,4-disubstituted, 1,4-dihydro-5 H-tetrazole-5-one derivatives of the fentanyl family. The ethyl derivatives (**33**), alfentanil (R-39209) was selected for extensive clinical investigations and as a result of its characteristic physicochemical and pharmacokinetic properties, afforded this compound a unique position within the class of clinically useful narcotic analgesics.



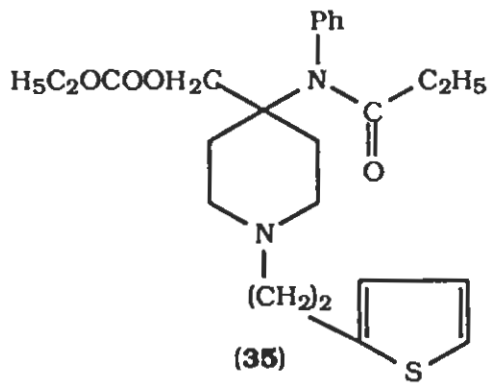
(33)

^{13}C-NMR studies on substituted 4-anilidopiperidines, which have a common calculated minimum energy conformation (Tollenaere and Janssen, 1988) have shown solution conformations similar to fentanyl (Brine *et al.*, 1989). *Para* substitution on the aniline group of fentanyl gives derivatives with potencies greater than morphine, although less than fentanyl itself (Casy and Huskstep, 1988a). Heterocyclic substitution for the phenyl ring has led to a potent opiate agonist (**34a**) and a novel antagonist (**34b**), which reverses both morphine-induced analgesia and respiratory depression (Bagley *et al.*, 1989). Notably ,one 4-(hetero-anilido) piperidine (**34c**) possesses a good analgesic profile in several animals models, with little cardiovascular and respiratory depression compared

to fentanyl. An anilinopiperidine 4-carbonate derivative (**35**) is potent and long acting (Colapret *et al.*, 1989). Several 4-phenyl and 4-heteroaryl-4-anilidopiperidines possess high analgesic potency and favourable pharmacological profiles (Kudzma *et al.*, 1989 and Feldman *et al.*, 1991).



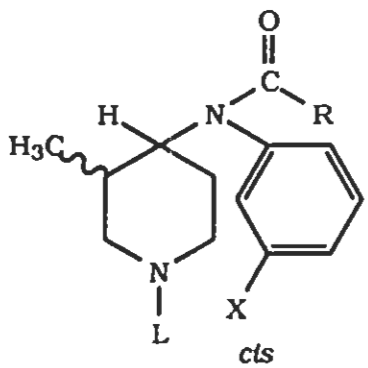
(34)



(35)

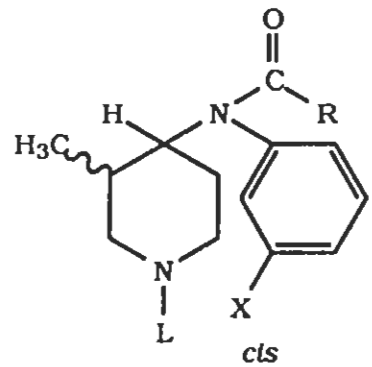
Lalinde *et al.*, (1990) synthesized a series of racemic cis and trans streoisomers of 3-methyl-4-anilidopiperidine in order to develop therapeutically advantageous analgesics with rapid onset and short duration of action. The effect caused by changing propionyl group to a methoxyacetyl was evaluated, since this substitution is known to confer short duration of action in 4-anilidopiperidine analgesics (Huang *et al.*, 1986). Among the resultant active compounds, *cis*-**36** was 13036 times more potent than morphine and 29 times more potent than fentanyl; however, the corresponding diastereoisomer

trans-**36** was only 2278 and 6 times more potent respectively. Compound (Anaquest A-3331 HCl, Brifentanil, *cis*-**37**) was selected for further clinical evaluations.



cis
L = thienylethyl
R = CH_2OCH_3
X = F

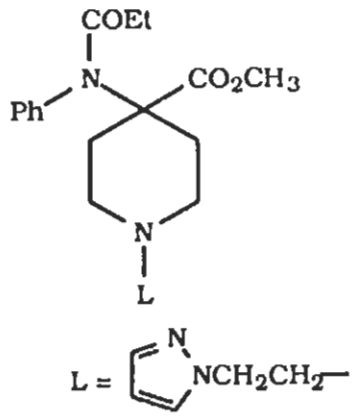
(36)



cis
L = tetrazolyethyl
R = CH_2OCH_3
X = F

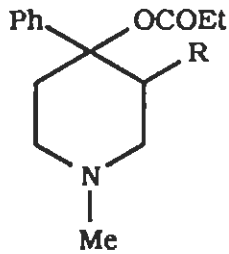
(37)

In another similar attempt, a series of new 1-(heterocycloalkyl)-4-piperidinyl methyl esters and methyl ethers have been synthesized and pharmacologically evaluated (Bagley *et al.*, 1991). In the mouse hot plate test, the majority of compounds exhibited an analgesia (ED_{50} <1 mg/kg) superior to that of morphine. Compound methyl 1-[2-(1H-pyrazol-1-yl)-ethyl]-4-[(1-oxopropyl) phenylamino]-4-piperidine carboxylate (**38**), which exhibited appreciable μ-opioid receptor affinity, was more potent and short-acting analgesic than alfentanil with less respiratory depression in the rat.



(38)

The effect of alkyl substitution in the piperidine ring of 4-phenylpiperidine analgesics has attracted much interest ever since the 3-methyl analogues of the reversed ester of meperidine were described in the late 1940s (Randall and Lehman, 1948). Since that time many 3-alkyl and all possible mono and nongeminal di-c-methyl derivatives of reversed ester have been reported, and much data have accrued on potency variations among isomeric sets and their relative and absolute geometries. In an analysis of these results (Casy *et al.*, 1982) a consistent stereochemical structure-activity pattern was developed on the basis of 4-phenylpiperidine ligands associating with the opiate receptors in the form of equatorial 4-phenyl chair conformations.



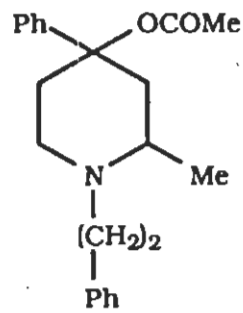
a) Alpha prodine, R = Me, 3-Me/4-Ph *trans*
b) Beta prodine, R = Me, 3-Me/4-Ph *cis*
c) Allyl prodine, R = $CH_2CH{:}CH_2$

(39)

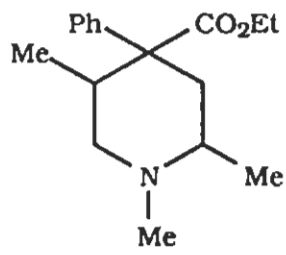
Methyl substitution in the 3- position is advantageous and leads to the potent compounds, alpha and beta prodine (Randall and Lehman, 1948, **39**). The observed enhanced activity of alpha prodine over that of pethidine in animals has been confirmed in man (40-60mg of alpha prodine is equivalent to 100mg of pethidine, Bachrach *et al.*, 1955).

High activity is also associated with ethyl and *N*-propyl groups substituted in the 3- position but is lost if the substituent be large (for example benzyl, McElvain and Barnett, 1956). The 3-allyl analogous (allyl prodine, **39c**) has been reported to be ten times as active as alpha prodine in rats but twice as toxic (Benson *et al.*, 1957). The only example of 2-methyl substitution available (**40**) is 1/5 as active as the unsubstituted analogue; the latter (several times as potent as morphine in mice) is somewhat more active than the 2,6-dimethyl

compound (Balon, 1959). 3,5-Dimethyl analogues are inactive while the 2,5-dimethyl compounds of Nazarov are highly active (Nazarov *et al.*, 1949). Trimeperidine (promedol, **41**) is reported to be several times more active than pethidine in animals (Nazarov *et al.*, 1952).



(40)



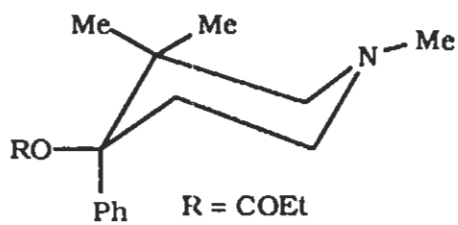
(41)

Similarly, in another paper (Ahmed *et al.*, 1985) described the preparation and resolution of 1,3,3-trimethyl-4-phenyl-4-(propionyloxy)piperidine (**42**) and the results of the antinociceptive activities of the products by hot plate (mice) and tail withdrawal test (rats) are shown to support proposals made from the stereochemical structure-activity relationships of C-methyl derivatives of the reversed ester of meperidine.

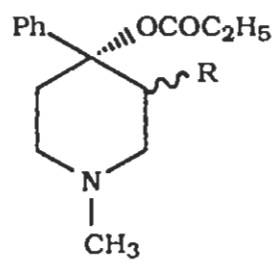
4-Phenylpiperidine analgesics which have piperidine chairs with an axial phenyl substituent as favoured conformation are rare but not unknown. Since these analgesics are complicated

by conformational difference among the substituents, therefore

structure-action relationships in substituted 4-phenylpiperidines are not easy to establish. The influence of stereochemical factors in reversed esters of 4-hydroxypiperidine is reflected in the wide potency differences found among geometric isomers such as trimeperidine and isopromedol (Mashkovskii and Abramova, 1956) and alpha and beta prodine type compounds (Beckett *et al.*, 1959 and Randall and Lehman, 1948).



(42)



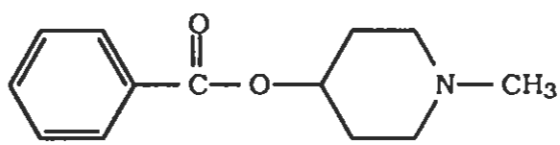
a) R = H
b) R = CH_3 *trans* to 4-Ph

(43)

Much work on the stereochemistry of analogues alkylated at piperidine ring carbon atoms has been reported that is helping to build a picture of the complex requirements of opiate receptors in relationship to 4-phenylpiperidine ligands. It has long been known that potency of parent ester (**43**) is little changed after insertion of 3-methyl trans to 4-phenyl (as in α-prodine, **39a**) but is elevated several folds when the

substituent is cis to the aromatic group (as in β-prodine, **39b**). It has only recently been appreciated, however, the case of methyl is unique and in pairs with larger alkyl substituents, the α-isomer (trans 3-R, 4-ph) is the more potent (Iorio *et al.*, 1975). Receptor affinities measured by determining the concentration of 3-alkylated ester to displace 50 % of specifically bound (H) dihydromorphine from rat brain homogenates have confirmed the higher affinity of β-over α- (*cis*-**43b**, R=Me) and α-over β (*trans*-**43b**), and results correlate well with analgesic potencies (Iorio and Klee, 1977).

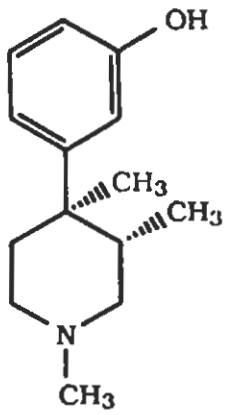
Substituted benzoic acid esters of 1-methyl-4-piperidinol (**44**) (Cheng *et al.*, 1982) showed analgesic activity when assayed by mouse hot plate method, the more potent one falling in the morphine-codeine range, but generally, they displayed no morphine like physical dependence liability in monkeys.



(44)

Research interests in piperidine analgesics have been focused on both experimental and theoretical studies in various alkyl, aryl and anilido structural classes. Energy conformational

calculation and X-rays crystallography on a series of flexible 4-alkyl-4-(3-phenyl)piperidines have been used to describe a "Universal phenyl axial pharmacophore" which gives high affinity μ-receptor binding (Loew *et al.*, 1988). NMR spectral studies have confirmed that 4-alkyl-4-(3-hydroxy or 3-methoxyphenyl) piperidines preferring the axial 4-aryl chair conformation are opiate agonists, whereas an antagonist was found to favour an equatorial 4-aryl chair (Casy *et al.*, 1989), also preferred in C-4 hydrogen and C-4 reversed ester analogues. Picenadol (**45**), a mixed opiate agonist/antagonist without psychomimetic effects, is being studied clinically for postoperative pain (Casy, 1988b). Among constrained 4-phenylpiperidines, the benzofuropyridine (**46**) has potent antinociceptive activity *in vivo* with a 2000-fold μ/*k*-selectivity (Hutchinson *et al.*, 1989) and 3-hydroxyphenyl substituted diazabicyclanes (**47**) are significantly more active than morphine as analgesics in mice (Salva *et al.*, 1986). Novel *N*-butyrophenone prodine analogues have displayed opiate analgesic and neuroleptic activity (Iorio *et al.*, 1987).



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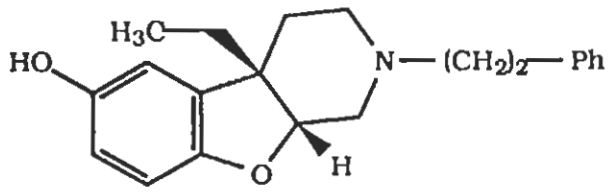

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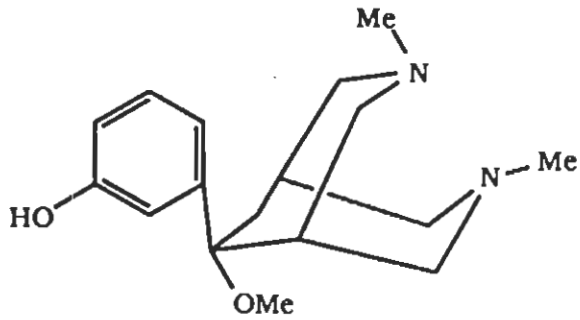
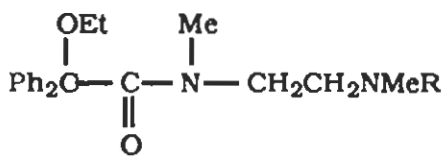


(47)

A number of novel structures containing quaternary diphenyl carbon centre, as in methadone, have been described (Casy, 1969). Certain basic amides (**48**) of *O*-ethylbenzilic acid are active by mouth in mice and rats. The most active members are somewhat more potent than pethidine and carry β-arylethylamino *N*-substituents such as phenethyl and 2-(or 4) pyridylethyl, structurally the amide (**48**) bear some resemblance to diampromid and other basic anilides but are best considered as mild analgesics since their effective oral dose in man is high (150 mg, Krapcho and Turk, 1963). The

derivatives (**49**) in which part of the methadone side chain has been incorporated into piperidine ring, is also reported as a potent analgesic (Newberne *et al.*, 1967).

Janssen has linked the cyanide precursor of normethadone to norpethidine to produce diphenoxylate (**50**), this complex is not an analgesic but has the constipating action of morphine derivatives and is used as antidiarrhoeal agent (Janssen *et al.*, 1962a,b and 1959b). The related 4- aminocarboxamide (**51**), piritramide (pirinitramide), obtained from *N*-benzyl-4-piperidone via the cyano-amine is an analgesic however, and is twice as active as morphine in mice (Janssen *et al.*, 1961).



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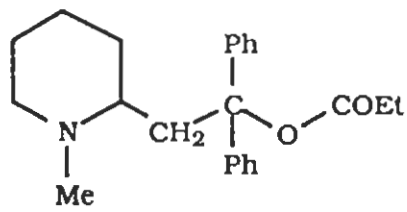

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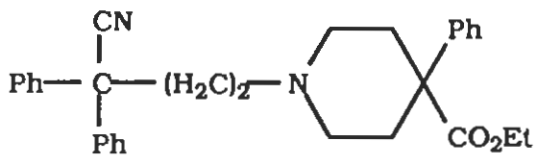

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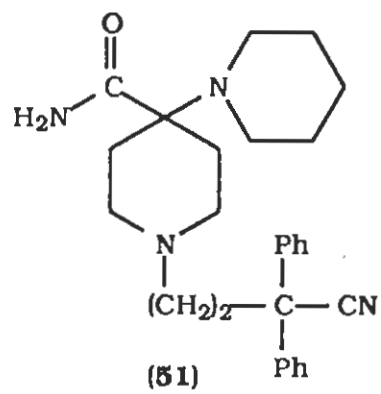
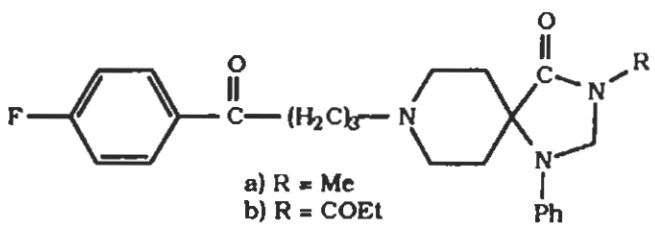


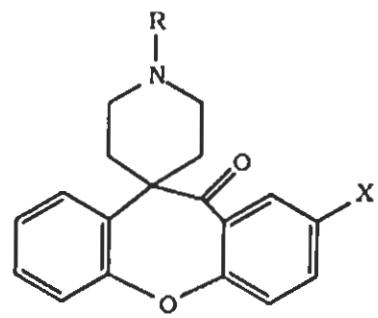
(51)

Several spiranes such as **52**, obtained by condensing 4-anilino analogues of **51** with formamide (Janssen, 1962c and 1965) have low hot plate ED_{50} values in mice; behave as powerful chlorpromazine-like sedatives in mice and monkeys. Although significant analgesic activity has been reported for a number of psychotropic agents with linear, tricyclic structure (Witiak *et al.*, 1976, Davis *et al.*, 1967 and Jilek *et al.*, 1965), compounds of this type, in general, have rarely been investigated clinically as analgetics because of their diverse



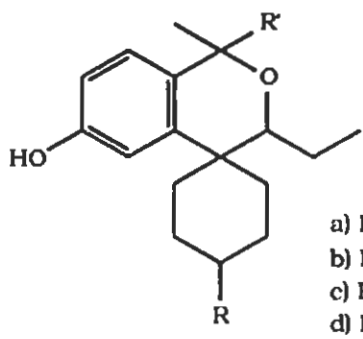
a) R = Me
b) R = COEt

(52)



X = H, F or Cl; R = H, alkyl, cycloalkyl or aralkyl
a) X = F, R = H

(53)



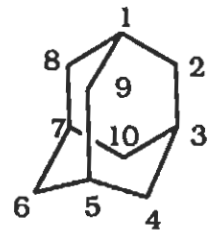
a) R = CH_3; R' = CH_3
b) R = $(CH_2)_4CH_3$; R' = CH_3
c) R = $(CH_2)_4CH_3$; R' = CH_2CH_3
d) R = $CH_2CH = CH_2$; R' = CH_3

(54)

pharmacological actions. Ong and Profitt (1979) synthesized a series of 10,11-dihydro-11-oxospiro [dibenz (b,f) oxepin-10,4'-

piperidine] derivatives (**53**) and evaluated for analgesic activity in the PQW assay and the tail flick test in mice. The compound **53a**, when administered orally, was equipotent to morphine in protecting against mouse writhing. Spiro analogues (**54**) of the potent narcotic ketobemidone have been prepared and found to be devoid of opiate activity (Rogers *et al.*, 1980).

The pronounced lipophilic nature associated with highly symmetrical, cage-like adamantane molecule (**55**, Landa *et al.*, 1933) invites a study of it's influence on characteristics and biological potential of compounds which contain this unique hydrocarbon moiety. It has been stated (Rall and Zubrod, 1962) that the characteristics of a high degree of lipoid solubility, low extent of ionization and lack of plasma protein binding virtually ensure that a compound will enter brain and cerebrospinal fluid freely and attain equilibrium rapidly. Adamantyl group in the synthesis of diverse classes of medicinal agents (Gerzon *et al.*, 1963 and 1967, Rapala *et al.*, 1965). has been utilized in a hope that adamantane derivative might fulfill these criteria and thus penetrate the tissues and fluids in the CNS.

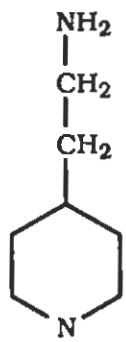


(55)

Various adamantane alkaneamines were prepared (Chakrabarti *et al.*, 1974) and their activity in antagonizing reserpine - induced hyperthermia was compared with nortriptyline. The anti-Parkinson activity possessed by some of these potent amines in reversing the reserpine-induced catalepsy in rats was equivalent to or better than amantadine. Similarly, Henkel *et al.*, (1982) synthesized a limited series of bridgehead alkyl-, dialkyl- and trialkyl-substituted amantadines and tested for potential anti-Parkinson activity as a dopamine (DA) agonists. The activity with in the series is dependent upon lipophilicity.

Apart from analgesics, a wide range of therapeutic agents are available in which piperidine nucleus is present. Specially hypotensive agents belonging to piperidine class of compounds are very important. The preparation of compounds of hexamethonium type in which the alkylene chain is incorporated in a cyclic structure was first reported by Norton (1953) and Phillips (1954). McMillan and Co-workers (1956)

later prepared a variety of cyclic derivatives, both aromatic and heterocyclic, and found some compounds to possess hypotensive activity comparable to that of hexamethonium. Phillips (1957) has also reported on derivatives of 4-(2-aminoethyl) piperidine (**56**) and 4-(3-aminopropyl) piperidines (**57**). In each of these series certain of the diamines and *bis*-quaternary salts exhibited pronounced ganglionic blockade in cats.



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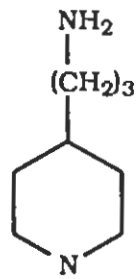
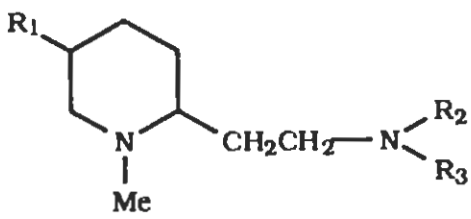


(57)

Shapiro and co-workers (1958 and 1960) have shown that the introduction of an oxygen atom into the alkyne side chain of structures of the type prepared by Phillips may also produce compounds having hypotensive, notably 2-(2-dialkylamino-ethoxy)-methyl-1-methylpiperidines and 2-(3-dimethylamino-propoxy)-1-methylpiperidines, which show equal or better activity as free amines than as their *bis*-quaternary salts. A series of 1-methyl-2-(2-aminoethyl) piperidine (**58**) and their



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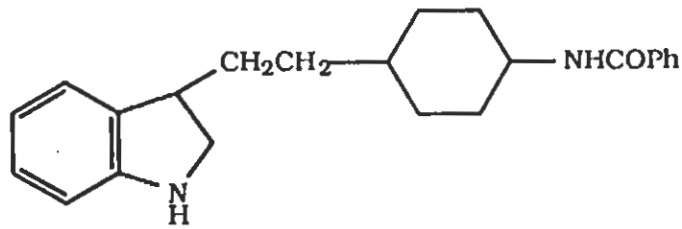


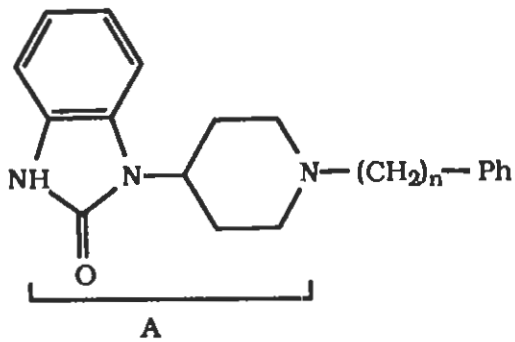
(59)

bis-quaternary ammonium salts have been prepared, evaluated and found hypotensive agents of the ganglionic blocking type (Minor *et al.*, 1962).

The continuing interest in the indole derivatives incorporating a tryptamine residue as potential antihypertensive agents stemmed from the work of Archibald *et al.*, (1970) with 1,4-*bis* (indolylethyl) piperidine. In that series, the indolylethyl moiety attached to the piperidine 4-position was not an essential feature for retention of antihypertensive activity. It could, for instance, be replaced without any detriment by a 3-carbethoxy-2,4-dimethylpyrrol-5-ylethyl group (Archibald *et al.*, 1966). While retaining the indolylethylpiperidine of the earlier series and varying the 4-substituents of the piperidine ring resulted in the discovery of 4- benzamidopiperidine derivative (indormin, **59**) as a potent hypotensive agent (Archibald *et al.*, 1971). This compound, then became the prototype for extensive synthetic programme designed to

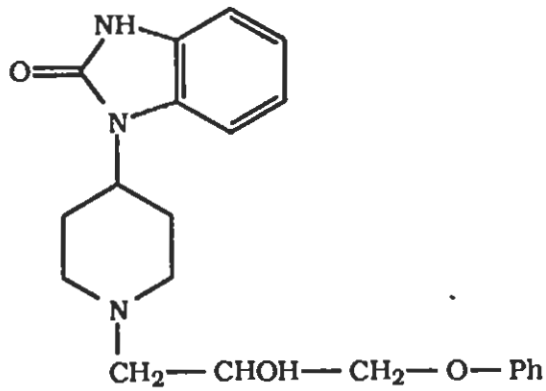
investigate structure-activity relationships and to optimize activity.

Many compounds having a structure which includes three or four methylene groups between a phenyl ring and the nitrogen atom of a piperidine ring have been synthesized in attempts to find new neuroleptics. However, only a few examples of Type I and II (**60** and **61**) compounds are found in the literature (Janssen, 1967). Obase *et al.*, (1982) designed compounds of the type III (**62**) on the basis of consideration that the bioavailability of methyldopa is known to be very low (Scriabine *et al.*, 1980) and methyldopa derivatives (which are more efficiently absorbed) might show higher antihypertensive potency and secondly, methyldopa is widely thought to be a centrally acting antihypertensive agent, and the 4-piperidylbenzamidazolinone group is likely to have high affinity for CNS. Benzamidazolinone derivatives of type III which contain a methyldopa moiety showed only moderate antihypertensive activity in three hypertensive rat models.

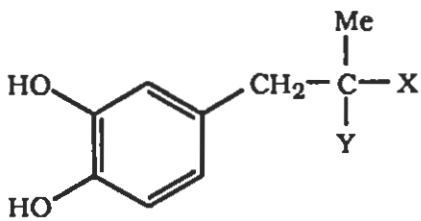


n = 1-2

I **(60)**



II **(61)**



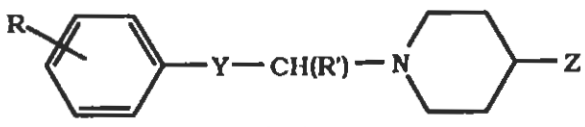
III **(62)**

i) X: NH_2, CoA, $CONHCH_2CoA$
ii) X: COOR (R = H or CH_3),
Y: $NHCOCH_2A$, $NHCO(CH_2)_2CoA$

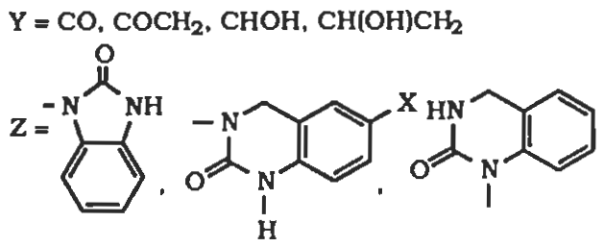
In a similar attempt, Takai *et al.*, (1985a) prepared a series of piperidine derivatives (**63**) with various heterocyclic rings at the 4-position and tested for antihypertensive activity and other biological activities. The antihypertensive effects of the present compounds in the spontaneous hypertensive rats were less potent than those of previously reported compounds.

Preparation of a series of 1 and 3-(1-substituted 4-piperidinyl) 1,2,3,4 tetrahydro-2-oxoquinazolines for anti-hypertensive studies showed that among the compounds

tested, 1-(2-hydroxy-2-oxo-3-quinazolinyl) piperidine derivatives were generally the most effective in lowering blood pressure in SHR (Takai *et al.*, 1985b).



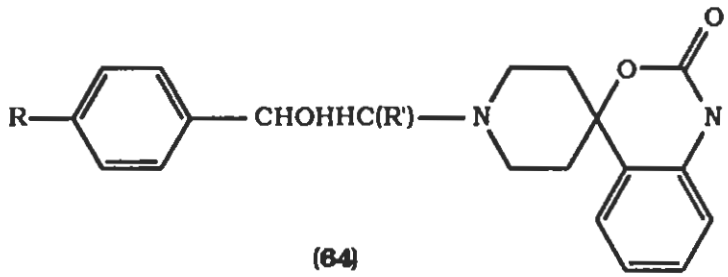
(63)



Several reports have appeared on antihypertensive piperidine derivatives (**64**) with a heterocyclic ring in the spiro form (Maillard *et al.*, 1970, 1972, 1973 and 1974, Klioze and Novick 1978, Caroon *et al.*, 1981, Clark *et al.*, 1983). Takai *et al.*, (1985c) selected the spiropiperidine for further modification and resulting derivatives were evaluated for antihypertensive activity. Most of the compounds synthesized in this study showed strong hypotensive activities both in SHR and in normotensive rats. Moreover, among these compounds, several were found to produce a very large and long lasting decrease in blood pressure.

Very potent and competitive β-adrenergic antagonists (**65**), derived from (aryloxy) propanolamine β-blockers through introduction of a piperidine ring were introduced by Mauleon

et al., (1988). This structural variation does not seem to markedly affect neither potency nor cardioselectivity, although one derivative was significantly more potent than propanalol.



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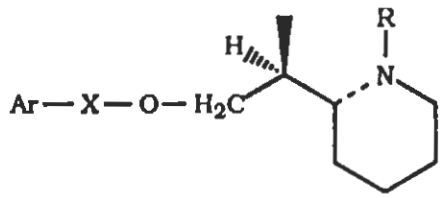


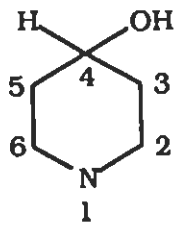
(65)

In view of the therapeutic potential as well as the pharmacological significance of various piperidine derivatives noted in the foregoing review, it was considered of interest to synthesize substituted-N-phenacyl derivatives of piperidines through simple quaternization reaction. The resulting derivatives were evaluated for analgesic activity and a few selected derivatives, among these, were examined for their effects on brain monoamines levels in male albino mice. The derivatives were also screened for their effects on mean arterial blood pressure (MABP) in normotensive aneasthetized rats.

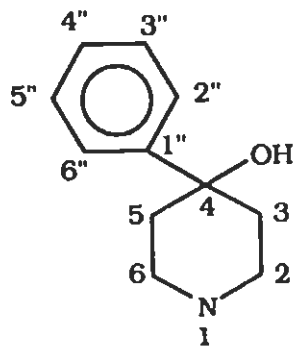
EXPERIMENTAL

GENERAL NOTE

Melting points were determined on Buchi 535 melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on Bruker AM 300, 400 and 500 spectrometers operating at 300, 400 and 500 MHz respectively. The chemical shifts are reported in δ(ppm) and coupling constants in Hz. IR and UV spectra were measured on JASCO IRA-1 and Pye-Unicam SP-800G spectrometers respectively. Mass spectra were recorded on Finnigan MAT 312, Variant MAT-112 double focussing mass spectrometers connected to PDP 11/34 (DEC) computer system. Purity of the products was checked on T.L.C. plates coated with silica gel 60 PF_{254} and the spots were visualized under ultraviolet light at 254 and 366 nm and by spraying iodine vapours.



(I)



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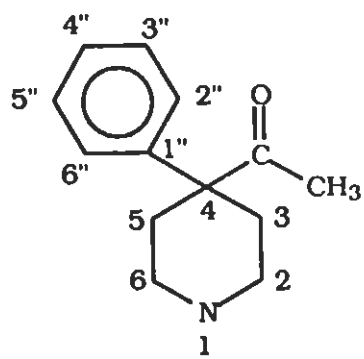


(III)

SYNTHESIS OF PIPERIDINE DERIVATIVES

Equimolar quantities of 4-hydroxypiperidine or 4-hydroxy-4-phenylpiperidine or 4-acetyl-4-phenylpiperidine and substituted phenacyl halides or 1-adamantyl bromomethyl ketone were dissolved in acetone, mixed together in a round bottom flask and refluxed on water bath until completion of the reaction.

Conversion of reactants into product was monitored by T.L.C. in different combinations of CH_3Cl-MeOH. When almost all the reactants changed to product, the resulting precipitate was collected by filtration, washed with cold acetone and recrystallized from appropriate solvent. The physical properties of these derivatives are presented in Tables 1-4.

CHARACTERIZATION OF COMPOUNDS:-

1-(4'-Methylphenacyl)-4-hydroxypiperidinium bromide (IV)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.94 (2H, d, J=8.30 Hz, H-2',6'), 7.36 (2H, d, J=8.30 Hz, H-3',5'), 6.02 (2H, s, H-α), 3.12 (3H, m, H-2,6), 2.43 (3H, s, Ar-CH_3), 2.05 (1H, m, H-4) and 1.76 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 233 (M^+-HBr, $C_{14}H_{19}NO_2$, 1), 135 (19), 120 (2), 114 (100), 105 (1), 91 (25), 84 (3), 76 (1) and 56 (90).

IR ν_{max} ($CHCl_3$) cm^{-1}: 3400, 2850, 1655, 1590, 1235 and 825.

UV λ_{max} (MeOH) nm: 256, 202 and 193.

1-(3'-Methoxyphenacyl)-4-hydroxypiperidinium bromide (V)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.63 (1H, ddd, J=7.70, 2.50, 1.80 Hz, H-6'), 7.52 (1H, dd, J=2.50, 1.65 Hz, H-2'), 7.47 (1H, t, J=8.05 Hz, H-5'), 7.25 (1H, ddd, J=8.05, 2.50, 1.80 Hz, H-4'), 6.24 (2H, s, H-α), 3.86 (3H, s, Ar-OCH_3), 3.12 (4H, m, H-2,6), 2.14 (1H, m, H-4) and 1.91 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 249 (M^+-HBr, $C_{14}H_{19}NO_3$, 1), 135 (39), 114 (100), 107 (26), 105 (1), 92 (15), 86 (12), 82 (10), 77 (26) and 56 (11).

IR ν_{max} ($CHCl_3$) cm^{-1}: 3650, 3300, 1720, 1690, 1590, 1230 and 985.

UV λ_{max} (MeOH) nm: 254, 220 and 201.

1-(4'-Methoxyphenacyl)-4-hydroxypiperidinium bromide (VI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.01 (2H, d, J=7.31 Hz, H-2',6'), 7.07 (2H, d, J=7.31 Hz, H-3',5'), 6.28 (2H, s, H-α), 3.90 (3H, s, Ar-OCH_3), 3.28 (4H, m, H-2,6), 2.14 (1H, m, H-4) and 1.91 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 249 (M^+-HBr, $C_{14}H_{19}NO_3$, 6), 150 (1), 120 (2), 114 (100), 100 (8), 92 (2), 82 (13), 80 (14), 77 (3) and 56 (2).

IR ν_{max} (KBr) cm^{-1}: 3300, 2900, 1660, 1585, 1250, 1160 and 820.

UV λ_{max} (MeOH) nm: 284, 222 and 202.

1-(2',4'-Dimethoxyphenacyl)-4-hydroxypiperidinium bromide (VII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.80 (1H, d, J=8.18 Hz, H-6'), 6.60 (1H, dd, J=8.18, 2.28 Hz, H-5'), 6.58 (1H, d, J=2.28 Hz, H-3'), 6.25 (2H, s, H-α), 3.92 (3H, s, Ar-OCH_3), 3.86 (3H, s, Ar-OCH_3), 3.21 (4H, m, H-2,6), 2.72 (1H, m, H-4) and 1.81 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 279 (M^+-HBr, $C_{15}H_{21}NO_4$, 1), 180 (6), 151 (4), 135 (2), 114 (100), 100 (12), 96 (5), 84 (2), 82 (15) and 56 (4).

IR ν_{max} ($CHCl_3$) cm^{-1}: 3300, 2800, 1720, 1660, 1600, 1420, 1180 and 990.

UV λ_{max} (MeOH) nm: 270, 226 and 203.

1-(2',5'-Dimethoxyphenacyl)-4-hydroxypiperidinium bromide (VIII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.50 (1H, d, J=3.25 Hz, H-6'), 7.26 (1H, dd, J=9.14, 3.25 Hz, H-4'), 7.17 (1H, d, J=9.14 Hz, H-3'), 6.19 (2H, s, H-α), 3.97 (3H, s, Ar-OCH_3), 3.79 (3H, s, Ar-OCH_3), 3.10 (4H, m, H-2,6), 2.12 (1H, m, H-4) and 1.75 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 279 (M^+-HBr, $C_{15}H_{21}NO_4$, 25), 180 (14), 165 (12), 151 (5), 114 (100), 100 (7), 82 (12), 77 (2) and 56 (1).

IR ν_{max} ($CHCl_3$) cm^{-1}: 3650, 3300, 1670, 1600, 1460 and 970.

UV λ_{max} (MeOH) nm: 350, 256 and 202.

1-(3',4'-Dihydroxyphenacyl)-4-hydroxypiperidinium chloride (IX)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.45 (1H, dd, J=8.82, 2.18 Hz, H-6'), 7.43 (1H, d, J=2.18 Hz, H-2'), 6.87 (1H, d, J=8.82 Hz, H-5'), 6.16 (2H, s, H-α), 3.29 (4H, m, H-2,6), 2.11 (1H, m, H-4) and 1.90 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 251 (M^+-HCl, $C_{13}H_{17}NO_4$, 1), 137 (4), 123 (2), 114 (100), 100 (8), 84 (3), 81 (2) and 56 (7).

IR ν_{max} (KBr) cm^{-1}: 3440, 2950, 1665, 1590, 1300, 1200 and 810

UV λ_{max} (MeOH) nm: 234, 222 and 208.

1-(4'-Phenylphenacyl)-4-hydroxypiperidinium bromide (X)

^{1}H-NMR (CD_3OD, 500 MHz) δ: 8.11 (2H, d, J=8.65 Hz, H-2'6'), 7.85 (2H, d, J=8.65 Hz, H-3'5'), 7.70 (2H, dd, J=8.45, 1.45 Hz, H-2",6"), 7.49 (2H, dt, J=8.45, 1.50 Hz, H-3",5"), 7.42 (1H, dd, J=8.45, 1.45 Hz, H-4"), 6.23 (2H, s, H-α), 3.15 (4H, m, H-2,6), 2.17 (1H, m, H-4) and 1.89 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 295 (M^+-HBr, $C_{19}H_{21}NO_2$, 2), 181 (2), 114 (100), 100 (4), 84 (2), 80 (7) and 56 (3).

IR ν_{max} (KBr) cm^{-1}: 3350, 2900, 1680, 1600, 1380 and 780.

UV λ_{max} (MeOH) nm: 289, 265 and 203.

1-(4'-Bromophenacyl)-4-hydroxypiperidinium bromide (XI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.94 (2H, d, J=8.80 Hz, H-2',6'), 7.76 (2H, d, J=8.80 Hz, H-3',5'), 6.12 (2H, s, H-α), 3.09 (4H, m, H-2,6), 2.14 (1H, m, H-4) and 1.73 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 299 (M^+-Br, $C_{13}H_{17}BrNO_2$, 2), 183 (2), 114 (100), 82 (14), 80 (15), 70 (3) and 56 (3).

IR ν_{max} (KBr) cm^{-1}: 3350, 2900, 1680, 1570, 1390, 1060 and 800.

UV λ_{max} (MeOH) nm: 261, 203 and 194.

1-(4'-Chlorophenacyl)-4-hydroxypiperidinium bromide (XII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.02 (2H, d, J=8.83 Hz, H-2',6'), 7.60 (2H, d, J=8.83 Hz, H-3',5'), 6.39 (2H, s, H-α), 3.36 (4H, m, H-2,6), 2.15 (1H, m, H-4) and 1.81 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 254 (M^+-Br, $C_{13}H_{17}ClNO_2$, 1), 139 (13), 114 (100), 101 (2), 84 (3), 82 (11) and 57 (6).

IR ν_{max} (KBr) cm^{-1}: 3300, 2900, 1675, 1565, 1250, 1045 and 820.

UV λ_{max} (MeOH) nm: 256, 230 and 203.

1-(4'-Fluorophenacyl)-4-hydroxypiperidinium chloride (XIII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.11 (2H, dd, J=9.03, 5.28 Hz, H-2',6'), 7.32 (2H, t, J=9.03 Hz, H-3',5'), 6.18 (2H, s, H-α), 3.22 (4H, m, H-2,6), 2.15 (1H, m, H-4) and 1.90 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 237 (M^+-HCl, $C_{13}H_{16}FNO_2$, 1), 123 (7), 114 (100), 101 (15), 100 (6), 96 (2), 84 (6), 82 (3) and 56 (18).

IR ν_{max} (KBr) cm^{-1}: 3300, 2900, 1675, 1580, 1230, 1050 and 840.

UV λ_{max} (MeOH) nm: 250, 204 and 192.

1-(4'-Methylphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XIV)

^{1}H-NMR (CD_3OD, 300 MHz) δ: 7.95 (2H, d, J=8.22 Hz, H-2',6'), 7.55 (2H, d, J=8.22 Hz, H-3',5'), 7.51 (2H, dd, J=8.54, 1.27 Hz, H-2",6"), 7.39 (2H, t, J=7.36 Hz, H-3",5"), 7.27 (1H, dd, J=8.26, 1.27 Hz, H-4"), 6.48 (2H, s, H-α), 3.42 (2H, ddd, J=12.98, 9.75, 4.36 Hz, H-2_a,6_a), 2.57 (2H, ddd, J=12.98, 5.34, 2.79 Hz, H-2_b,6_b), 2.45 (3H, s, Ar-CH_3), 2.19 (2H, ddd, J=17.67, 9.75, 4.82 Hz, H-3_a,5_a) and 1.97 (2H, ddd, J=17.67, 4.36, 2.79 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 309 (M^+-HBr, $C_{20}H_{23}NO_2$, 1), 190 (100), 176 (2), 172 (28), 159 (27), 143 (3), 120 (3), 103 (16), 91 (17), 84 (15) and 77 (18).

IR ν_{max} (KBr) cm^{-1}: 3350, 2900, 1670, 1580, 970 and 755.

UV λ_{max} (MeOH) nm: 257 and 203.

1-(3'-Methoxyphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XV)

^{1}H-NMR (CD_3OD, 300 MHz) δ: 8.25 (1H, dd, J=7.53, 1.02 Hz, H-6'), 7.91 (1H, dd, J=2.45, 1.02 Hz, H-2'), 7.61 (1H, t,

J=8.02 Hz, H-5'), 7.50 (1H, dd, J=8.02, 1.02 Hz, H-4'), 7.41 (2H, dd, J=7.85, 2.16 Hz, H-2",6"), 7.39 (1H, t, J=7.99 Hz, H-3",5"), 7.28 (2H, dd, J=8.21, 2.16 Hz, H-4"), 6.24 (2H, s, H-α), 3.88 (3H, s, Ar-OCH_3), 3.40 (2H, dt, J=14.70, 4.21 Hz, H-2_a,6_a), 3.39 (2H, td, J=14.70, 5.00 Hz, H-2_b,6_b), 2.28 (2H, ddd, J=18.40, 14.70, 5.00 Hz, H-3_a,5_a) and 1.96 (2H, ddd, J=18.40, 5.00, 4.21 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 325 (M^+-HBr, $C_{20}H_{23}NO_3$, 2), 190 (100), 172 (17), 159 (2), 135 (3), 107 (2), 105 (4), 91 (6), 84 (9) and 77 (8).

IR ν_{max} (KBr) cm^{-1}: 3350, 2900, 1580, 1425, 1375 and 975.

UV λ_{max} (MeOH) nm: 251, 205 and 219.

1-(4'-Methoxyphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XVI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.05 (2H, d, J=8.97 Hz, H-2',6'), 7.55 (2H, d, J=8.97 Hz, H-3',5'), 7.50 (2H, dd, J=7.21, 1.18 Hz, H-2",6"), 7.38 (2H, t, J=8.05 Hz, H-3",5"), 7.28 (1H, dd, J=6.65, 1.18 Hz, H-4"), 6.36 (2H, s, H-α), 3.91 (3H, s, Ar-OCH_3), 3.44 (2H, dt, J=14.73, 3.19 Hz, H-2_a,6_a), 2.49 (2H, td,

J=14.73, 4.62 Hz, H-2_b,6_b), 2.24 (2H, ddd, J=18.08, 14.73, 4.62 Hz, H-3_a,5_a) and 1.95 (2H, ddd, J=18.08, 4.62, 3.19 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 325 (M^+-HBr, $C_{20}H_{23}NO_3$, 3), 190 (100), 176 (12), 172 (7), 159 (96), 135 (13), 103 (9), 82 (51) and 77 (50).

IR ν_{max} (KBr) cm^{-1}: 3350, 2900, 1685, 1580, 1260, 970 and 760.

UV λ_{max} (MeOH) nm: 205, 250 and 283.

1-(2',4'-Dimethoxyphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XVII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.02 (1H, d, J=9.43 Hz, H-6'), 7.55 (1H, dd, J=9.43, 1.34 Hz, H-5'), 7.51 (2H, dd, J=7.66, 1.57 Hz, H-2",6"), 7.36 (2H, t, J=8.36 Hz, H-3",5"), 7.28 (2H, dd, J=8.36, 1.57 Hz, H-4"), 6.68 (1H, d, J=1.34 Hz, H-3'), 6.20 (2H, s, H-α), 4.00 (3H, s, Ar-OCH_3), 3.91 (3H, s, Ar-OCH_3), 3.45 (2H, ddd, J=17.62, 12.82, 3.17 Hz, H-2_a,6_a), 2.54 (2H, dt, J=17.62, 5.00 Hz, H-2_b,6_b), 2.27 (2H, ddd, J=18.09, 12.82,

5.00 Hz, H-3_a,5_a) and 1.96 (2H, ddd, J=18.09, 17.62, 2.65 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 355 (M^+-HBr, $C_{21}H_{25}NO_4$, 2), 190 (100), 176 (24), 172 (20), 165 (13), 112 (7) and 84 (10).

IR ν_{max} (KBr) cm^{-1}: 3250, 2650, 1630, 1570, 1250, 970 and 750.

UV λ_{max} (MeOH) nm: 351, 273 and 202.

1-(2',5'-Dimethoxyphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XVIII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.54 (1H, d, J=2.32 Hz, H-6'), 7.49 (1H, dd, J=7.93, 1.17 Hz, H-2",6"), 7.39 (2H, t, J=7.25, H-3",5"), 7.29 (1H, dd, J=7.51, 1.17 Hz, H-4"), 7.26 (1H, dd, J=8.56, 1.37 Hz, H-4'), 7.18 (1H, d, J=9.14 Hz, H-3'), 6.00 (2H, s, H-α), 3.99 (3H, s, Ar-OCH_3), 3.88 (3H, s, Ar-OCH_3), 3.32 (2H, dt, J=14.75, 2.24 Hz, H-2_a,6_a), 2.45 (2H, dt, J=14.75, 4.41 Hz, H-2_b,6_b), 2.21 (2H, ddd, J=18.02, 14.75, 4.65 Hz, H-3_a,5_a) and 1.97 (2H, ddd, J=18.02, 4.41, 2.24 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 355 (M^+-HBr, $C_{21}H_{25}NO_4$, 2), 337 (2), 190 (100), 176 (2), 172 (74), 165 (9), 158 (25), 135 (2), 131 (4), 113 (7), 107 (7), 105 (8), 91 (13) and 77 (22).

IR ν_{max} (KBr) cm^{-1}: 3350, 2850, 1570, 1420, 960 and 750.

UV λ_{max} (MeOH) nm: 309, 274 and 205.

1-(3',4'-Dihydroxyphenacyl)-4-hydroxy-4-phenylpiperidinium chloride (XIX)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.56 (1H, dd, J=8.27, 1.35 Hz, H-6'), 7.52 (1H, d, J=1.35 Hz, H-2'), 7.48 (2H, dd, J=7.12, 2.25 Hz, H-2",6"), 7.40 (2H, t, J=7.92 Hz, H-3",5"), 7.30 (1H, dd, J=6.03, 2.25 Hz, H-4"), 6.90 (1H, d, J=8.60 Hz, H-5'), 6.38 (2H, s, H-α), 3.45 (2H, dt, J=14.70, 4.70 Hz, H-2_a,6_a), 2.49 (2H, dt, J=14.70, 2.85 Hz, H-2_b,6_b), 2.27 (2H, ddd, J=18.00, 14.44, 4.70 Hz, H-3_a,5_a) and 1.98 (2H, ddd, J=18.00, 14.70, 2.85 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 327 (M^+-HCl, $C_{19}H_{21}NO_4$, 1), 190 (100), 176 (4), 172 (21), 137 (5), 112 (7), 105 (4), 92 (5) and 84 (100).

IR ν_{max} (KBr) cm^{-1}: 3250, 2950, 1665, 1590, 1300, 1120 and 810.

UV λ_{max} (MeOH) nm: 283, 234 and 207.

1-(4'-Phenylphenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XX)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.14 (2H, d, J=8.56 Hz, H-2',6'), 7.85 (2H, d, J=8.56 Hz, H-3',5'), 7.70 (2H, dd, J=8.18, 1.46 Hz, H-2''',6'''), 7.56 (2H, dt, J=8.18, 1.46 Hz, H-3''',5'''), 7.50 (1H, dd, J=8.18, 1.46 Hz, H-4'''), 7.45 (2H, dd, J=6.40, 1.32 Hz, H-2",6"), 7.41 (2H, t, J=7.33 Hz, H-3",5"), 7.29 (1H, dd, J=8.04, 1.32 Hz, H-4"), 6.20 (2H, s, H-α), 3.44 (2H, ddd, J=17.42, 11.92, 3.82 Hz, H-2_a6_a), 2.61 (2H, dt, J=17.42, 5.41 Hz, H-2_b,6_b), 2.27 (2H, ddd, J=17.92, 11.92, 5.41 Hz, H-3_a,5_a) and 1.97 (2H, ddd, J=17.92, 5.41, 3.82 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 371 (M^+-HBr, $C_{25}H_{25}NO_2$, 1), 195 (3), 190 (100), 181 (14), 172 (20), 152 (9), 112 (14), 105 (8), 91 (13), 84 (29) and 77 (11).

IR ν_{max} (KBr) cm^{-1}: 3450, 1690, 1595, 1220, 950 and 780.

UV λ_{max} (MeOH) nm: 306, 290 and 201.

1-(4'-Bromophenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XXI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.20 (2H, d, J=8.62 Hz, H-2',6'), 7.62 (2H, d, J=8.62 Hz, H-3',5'), 7.51 (2H, dd, J=8.58, 1.38 Hz, H-2",6"), 7.36 (2H, t, J=7.98 Hz, H-3",5"), 7.26 (1H, dd, J=9.31, 1.38 Hz, H-4"), 6.68 (2H, s, H-α), 3.45 (2H, dt, J=13.96, 4.17 Hz, H-2_a,6_a), 3.34 (2H, ddd, J=13.96, 3.42, 2.34 Hz, H-2_b,6_b), 2.29 (2H, ddd, J=18.14, 13.96, 4.74 Hz, H-3_a,5_a) and 1.92 (2H, ddd, J=18.14, 4.17, 2.34 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 374 (M^+-HBr, $C_{19}H_{20}NO_2$, 1), 190 (100), 185 (12), 177 (8), 172 (17), 159 (37), 130 (15), 105 (34), 91 (17), 83 (27) and 77 (30).

IR ν_{max} (KBr) cm^{-1}: 3300, 2800, 1560, 1410, 980 and 750.

UV λ_{max} (MeOH) nm: 310, 259 and 203.

1-(4'-Chlorophenacyl)-4-hydroxy-4-phenylpiperidinium bromide (XXII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.07 (2H, d, J=8.66 Hz, H-2',6'), 7.61 (2H, d, J=8.66 Hz, H-3',5'), 7.51 (2H, dd, J=8.56, 1.38 Hz, H-2",6"), 7.36 (2H, t, J=8.00 Hz, H-3",5"), 7.27 (1H, dd,

J=8.00, 1.38 Hz, H-4"), 6.34 (2H, s, H-α), 3.47 (2H, dt, J=11.29, 3.16 Hz, H-2_a,6_a), 3.35 (2H, ddd, J=11.29, 4.75, 3.10 Hz, H-2_b,6_b), 2.30 (2H, ddd, J=18.11, 11.29, 4.75 Hz, H-3_a,5_a) and 1.92 (2H, ddd, J=18.11, 4.75, 3.16 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 329 (M^+-HBr, $C_{19}H_{20}ClNO_2$, 1), 190 (100), 177 (14), 172 (17), 159 (36), 156 (21), 141 (10), 112 (16), 91 (13) and 82 (11).

IR ν_{max} (KBr) cm^{-1}: 3250, 2900, 1675, 1580, 1380, 1080 and 810.

UV λ_{max} (MeOH) nm: 309, 225 and 201.

1-(4'-Fluorophenacyl)-4-hydroxy-4-phenylpiperidinium chloride (XXIII)

^{1}H-NMR (CD_3OD, 300 MHz) δ: 8.00 (2H, d, J=7.98 Hz, H-2',6'), 7.68 (2H, d, J=7.98 Hz, H-3',5'), 7.50 (2H, dd, J=8.37, 2.04 Hz, H-2",6"), 7.37 (2H, t, J=7.14 Hz, H-3",5"), 7.28 (1H, dd, J=6.90, 2.04 Hz, H-4"), 6.02 (2H, s, H-α), 3.45 (2H, dt, J=12.77, 4.32 Hz, H-2_a,6_a), 3.20 (2H, dt, J=12.77, 2.20 Hz, H-2_b,6_b), 2.22 (2H, ddd, J=18.09, 12.77, 4.32 Hz, H-3_a,5_a) and 1.92 (2H, ddd, J=18.09, 4.32, 2.20 Hz, H-3_b,5_b).

EIMS *m/z* (relative int., %): 313 (M^+-HCl, $C_{19}H_{20}FNO_2$, 1), 190 (100), 176 (18), 171 (15), 159 (14), 123 (5), 104 (14), 91 (11), 82 (11) and 77 (16).

IR ν_{max} (KBr) cm^{-1}: 3325, 2950, 2775, 1680, 1590, 1225, 980 and 690.

UV λ_{max} (MeOH) nm: 310, 247 and 205.

1-(4'-Methylphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXIV)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.91 (2H, d, J=8.31 Hz, H-2',6'), 7.48 (2H, d, J=8.31 Hz, H-3',5'), 7.37 (5H, m, H,2"-6"), 6.32 (2H, s, H-α), 2.89-2.65 (4H, m, H-2,6), 2.04-1.90 (4H, m, H-3,5), 2.43 (3H, s, Ar-CH_3) and 1.98 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 335 (M^+-HBr, $C_{22}H_{25}NO_2$, 1), 216 (100), 203 (1), 173 (6), 103 (5), 115 (4), 129 (5) and 82 (13).

IR ν_{max} (KBr) cm^{-1}: 3400, 2900, 2650, 1680 and 1340.

UV λ_{max} (MeOH) nm: 280, 258 and 203.

1-(3'-Methoxyphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXV)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.00 (1H, dt, J=8.02, 1.47 Hz, H-6'), 7.67 (1H, t, J=7.61 Hz, H-5'), 7.59 (1H, dd, J=2.50, 1.47 Hz, H-2'), 7.30 (5H, m, H,2"-6"), 7.13 (1H, ddd, J=7.61, 2.50, 1.47 Hz, H-4'), 6.25 (2H, s, H-α), 3.86 (3H, s, Ar-OCH_3), 2.98-2.66 (4H, m, H-2,6), 2.04-1.90 (4H, m, H-3,5) and 1.93 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 351 (M^+-HBr, $C_{22}H_{25}NO_3$, 6), 307 (2), 216 (100), 203 (14), 173 (5), 159 (10), 135 (3), 129 (6) and 82 (37).

IR ν_{max} (KBr) cm^{-1}: 3300, 2810, 2550, 1660 and 680.

UV λ_{max} (MeOH) nm: 204, 219 and 202.

1-(4'-Methoxyphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXVI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.98 (2H, d, J=9.02 Hz, H-2',6'), 7.38 (5H, m, H,2"-6"), 7.06 (2H, d, J=9.02 Hz, H-3',5'), 6.00 (2H, s, H-α), 3.89 (3H, s, Ar-OCH_3), 2.89-2.66 (4H, m, H-2,6), 2.01-1.95 (4H, m, H-3,5) and 1.99 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 351 (M^+-HBr, $C_{22}H_{25}NO_3$, 1), 273 (1), 216 (100), 202 (11), 173 (5), 158 (6), 135 (3), 129 (6) and 82 (37).

IR ν_{max} (KBr) cm^{-1}: 2900, 2650, 1800, 1580, 1150 and 960.

UV λ_{max} (MeOH) nm: 283, 219 and 201.

1-(2',4'-Dimethoxyphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXVII)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.88 (1H, d, J=8.78 Hz, H-6'), 7.31 (5H, m, H,2"-6"), 6.53 (1H, dd, J=8.78, 2.29 Hz, H-5'), 6.41 (1H, d, J=2.29 Hz, H-3'), 6.40 (2H, s, H-α), 3.87 (3H, s, Ar-OCH_3), 3.84 (3H, s, Ar-OCH_3), 3.83-3.80 (4H, m, H-2,6), 2.57-2.40 (4H, m, H-3,5) and 1.93 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 381 (M^+-HBr, $C_{23}H_{27}NO_4$, 1), 336 (4), 259 (3), 217 (15), 216 (100), 202 (18), 173 (6), 165 (30), 159 (7), 129 (6) and 82 (37).

IR ν_{max} (KBr) cm^{-1}: 2800, 2500, 1570, 1430, 1240 and 940.

UV λ_{max} (MeOH) nm: 351, 256 and 203.

1-(2',5'-Dimethoxyphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXVIII)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.47 (1H, d, J=3.21 Hz, H-6'), 7.25 (5H, m, H,2"-6"), 7.14 (1H, dd, J=9.09, 3.21 Hz, H-4'), 6.93 (1H, d, J=9.09 Hz, H-3'), 6.31 (2H, s, H-α), 3.93 (3H, s, Ar-OCH_3), 3.79 (3H, s, Ar-OCH_3), 2.89-2.66 (4H, m, H-2,6), 2.04-1.99 (4H, m, H-3,5) and 1.98 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 381 (M^+ - HBr, $C_{23}H_{27}NO_4$, 2), 275 (1), 223 (2), 216 (100), 203 (17), 173 (6), 159 (13), 133 (1), 103 (8) and 83 (25).

IR ν_{max} (KBr) cm^{-1}: 3400, 2910, 2500, 1690, 1485, 1280 and 1060.

UV λ_{max} (MeOH) nm: 309, 274 and 202.

1-(3',4'-Dihydroxyphenacyl)-4-acetyl-4-phenylpiperidinium chloride (XXIX)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.48 (1H, dd, J=7.23, 1.2 Hz, H-6'), 7.42 (1H, d, J=1.2 Hz, H-2'), 7.36 (5H, m, H,2"-6"), 6.86 (1H, d, J=7.23 Hz, H-5'), 6.20 (2H, s, H-α), 3.46-3.39 (4H, m, H-2,6), 2.04-1.91 (4H, m, H-3,5) and 1.96 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 354 (M^+ - Cl, $C_{21}H_{24}NO_4$, 2), 216 (100), 203 (5), 173 (4), 157 (12), 121 (18), 111 (24), 105 (26) and 83 (70).

IR ν_{max} (KBr) cm^{-1}: 3330, 2650, 1660, 1590, 1300 and 810.

UV λ_{max} (MeOH) nm: 320, 265 and 204.

1-(4'-Phenylphenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXX)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.01 (2H, d, J=8.56 Hz, H-2',6'), 7.69 (2H, d, J=8.56 Hz, H-3',5'), 7.61 (2H, dd, J=8.42, 1.80 Hz, H-2"',6"'), 7.43 (5H, m, H,2"-6"), 7.37 (2H, dd, J=8.42, 6.63 Hz, H-3"',5"'), 7.29 (1H, dd, J=8.42, 1.80 Hz, H-4"'), 6.10 (2H, s, H-α), 3.46-3.39 (4H, m, H-2,6), 2.56-2.42 (4H, m, H-3,5) and 1.96 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 397 (M^+ - HBr, $C_{27}H_{27}NO_2$, 23), 352 (1), 216 (100), 203 (10), 173 (7), 159 (17), 152 (6), 129 (8), 115 (10) and 82 (20).

IR ν_{max} (KBr) cm^{-1}: 2900, 2750, 1680, 1590, 1240 and 950.

UV λ_{max} (MeOH) nm: 302, 292 and 204.

1-(4'-Bromophenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXXI)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 7.97 (2H, d, J=8.02 Hz, H-2',6'), 7.38 (2H, d, J=8.02 Hz, H-3',5'), 7.42 (5H, m, H,2"-6"), 6.15 (2H, s, H-α), 3.83-3.80 (4H, m, H-2,6), 2.57-2.40 (4H, m, H-3,5) and 1.93 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 400 (M^+-HBr, $C_{21}H_{22}BrNO_2$, 10), 216 (100), 203 (10), 185 (2), 173 (7), 158 (10), 129 (11), 115 (10), 103 (11) and 82 (25).

IR ν_{max} (KBr) cm^{-1}: 2800, 1685, 1560, 1360 and 815.

UV λ_{max} (MeOH) nm: 282, 261 and 202.

1-(4'-Chlorophenacyl)-4-acetyl-4-phenylpiperidinium bromide (XXXII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.00 (2H, d, J=8.64 Hz, H-2',6'), 7.60 (2H, d, J=8.64 Hz, H-3',5'), 7.40 (5H, m, H,2"-6"), 6.32 (2H, s, H-α), 2.89-2.65 (4H, m, H-2,6), 2.04-1.92 (4H, m, H-3,5) and 1.97 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 355 (M^+-HBr, $C_{21}H_{22}ClNO_2$, 1), 216 (100), 203 (5), 173 (7), 158 (6), 152 (2), 139 (4) and 83 (60).

IR ν_{max} (KBr) cm^{-1}: 3330, 2810, 2550, 1680, 1580 and 1230.

UV λ_{max} (MeOH) nm: 266, 254 and 201.

1-(4'-Fluorophenacyl)-4-acetyl-4-phenylpiperidinium chloride (XXXIII)

^{1}H-NMR (CD_3OD, 400 MHz) δ: 8.08 (2H, dd, J=8.98, 5.29 Hz, H-2',6'), 7.36 (5H, m, H,2"-6"), 7.28 (2H, t, J=8.98 Hz, H-3',5'), 6.30 (2H, s, H-α), 3.40-3.18 (4H, m, H-2,6), 1.96-1.94 (4H, m, H-3,5) and 1.92 (3H, s, $COCH_3$, C-4).

EIMS *m/z* (relative int., %): 339 (M^+-HCl, $C_{21}H_{22}FNO_2$, 1), 216 (100), 203 (22), 188 (5), 173 (7), 159 (20), 129 (8), 103 (8) and 83 (18).

IR ν_{max} (KBr) cm^{-1}: 2900, 2700, 1690, 1595, 1230 and 760.

UV λ_{max} (MeOH) nm: 272, 245 and 201.

1-(1-Adamantyl methyl ketone)-4-hydroxypiperidinium bromide (XXXIV)

^{1}H-NMR (CD_3OD, 300 MHz) δ: 6.25 (2H, s, H-α), 3.10 (4H, m, H-2,6), 2.07 (1H, m, H-4), 2.06 (3H, m, H-3',5',7'), 1.88 (6H, d, J=2.77 Hz, H-2',8',9'), 1.78 (6H, m, H-4',6',10) and 1.77 (4H, m, H-3,5).

EIMS *m/z* (relative int., %): 277 (M^+-HBr, $C_{17}H_{27}NO_2$, 1), 176 (2), 114 (100), 100 (2), 96 (1), 83 (5), 77 (1) and 57 (1).

IR ν_{max} (KBr) cm^{-1}: 3400, 2900, 1700, 1440 and 1050.

UV λ_{max} (MeOH) nm: 288 and 201.

1-(1-Adamantyl methyl ketone)-4-hydroxy-4-phenylpiperidinium bromide (XXXV)

^{1}H-NMR (d_6-DMSO, 300 MHz) δ: 7.48 (2H, dd, J=7.05, 2.20 Hz, H-2",6"), 7.39 (2H, t, J=7.08 Hz, H-3",5"), 7.28 (1H, dt, J=7.08, 2.20 Hz, H-4"), 6.24 (2H, s, H-α), 3.42 (2H, ddd, J=12.98, 9.64, 4.03 Hz, H-2_a,6_a), 2.54 (2H, ddd, J=12.98, 5.44, 2.92 Hz, H-2_b,6_b), 2.18 (2H, ddd, J=17.67, 9.64, 4.72 Hz, H-3_a,5_a), 2.02 (3H, m, H-3',5',7'), 1.97 (2H, ddd, J=17.67,

4.03, 2.92 Hz, H-3_b,5_b), 1.85 (6H, d, J=2.79 Hz, H-2',8',9') and 1.71 (6H, m, H-4',6'10').

EIMS *m/z* (relative int., %): 353 (M^+-HBr, $C_{23}H_{31}NO_2$, 1), 190 (100), 172 (13), 162 (1), 112 (6), 105 (5), 91 (6), 82 (5) and 77 (7).

IR ν_{max} (KBr) cm^{-1}: 3300, 2900, 1695, 1440, 1130 and 750.

UV λ_{max} (MeOH) nm: 303 and 202.

1-(1-Adamantyl methyl ketone)-4-acetyl-4-phenylpiperidinium bromide (XXXVI)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.43 (5H, m, H,2"-6"), 6.42 (2H, s, H-α), 3.37-3.30 (4H, m, H-2,6), 2.42-2.10 (4H, m, H-3,5), 2.08 (3H, s, $COCH_3$, C-4), 2.01 (3H, m, H-3',5',7'), 1.85 (6H, d, J=2.79 Hz, H-2',8'9') and 1.71-1.68 (6H, m, H-4',6',10').

EIMS *m/z* (relative int., %): 379 (M^+-HBr, $C_{25}H_{33}NO_2$, 1), 216 (62), 203 (29), 188 (5), 186 (5), 172 (2), 160 (27), 143 (2), 128 (6), 102 (12), 91 (22), 82 (24) and 57 (100).

IR ν_{max} (KBr) cm^{-1}: 3300, 2800, 1670, 1420, 1105 and 740.

UV λ_{max} (MeOH) nm: 297 and 201.

1-(1-Adamantyl methyl ketone)-2-ethanolpiperidinium bromide (XXXVII)

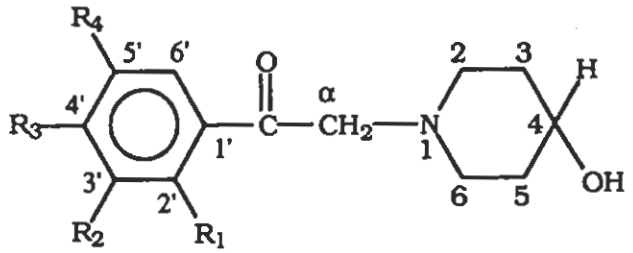
^{1}H-NMR (CD_3OD, 300 MHz) δ: 6.00 (2H, s, H-α), 3.75 (1H, ddd, J=19.48, 10.82, 5.07 Hz, H-6_a), 3.21 (2H, s, H-2"), 2.98 (1H, ddd, J=19.48, 5.07, 2.65 Hz, H-6_b), 2.70 (1H, m, H-2), 2.55 (2H, m, H-1"), 2.06-2.02 (3H, m, H-3',5',7'), 1.88 (6H, d, J=2.70, H-2',8',9'), 1.79 (6H, m, H-4',6',10') and 1.10-1.18 (6H, m, H-3,4,5).

EIMS *m/z* (relative int., %): 305 (M^+-HBr, $C_{19}H_{31}NO_2$, 1), 286 (25), 257 (14), 163 (3), 142 (58), 135 (63), 124 (100), 112 (70), 98 (52), 84 (1) and 57 (22).

IR ν_{max} (KBr) cm^{-1}: 3250, 2900, 1700, 1440, 1250 and 1030.

UV λ_{max} (MeOH) nm: 283, 202 and 192.

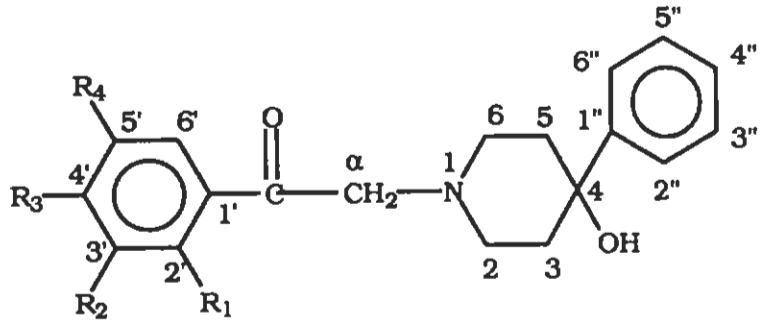
Table-1: Substitued Phenacyl Derivatives of 4-Hydroxypiperidine and Their Physical Data.



S. No.	Compund	R_1	R_2	R_3	R_4	Salt	Colour/Shape	M.P. (°C)	Mol. Formula	Yield (%)
1	IV	H	H	CH_3	H	HBr	Brown Gumy Matter	-	$C_{14}H_{20}BrNO_2$	72
2	V	H	OCH_3	H	H	HBr	Yellowish Semisolid	-	$C_{14}H_{20}BrNO_3$	67
3	V	H	H	OCH_3	H	HBr	Colourless Crystals	176-178	$C_{14}H_{20}BrNO_3$	64
4	VII	OCH_3	H	OCH_3	H	HBr	Dark Brown Oil	130-132	$C_{15}H_{22}BrNO_4$	58
5	VIII	OCH_3	H	H	OCH_3	HBr	Colourless Semisolid	-	$C_{15}H_{22}BrNO_4$	66
6	IX	H	OH	OH	H	HCl	Ash White Crystals	148-150	$C_{13}H_{18}ClNO_4$	78
7	X	H	H	Ph	H	HBr	Colourless Needles	212-215	$C_{19}H_{22}BrNO_2$	70
8	XI	H	H	Br	H	HBr	Colourless Rods	216-218	$C_{13}H_{17}Br_2NO_2$	72
9	XII	H	H	Cl	H	HBr	Light Yellow Plates	238-240	$C_{13}H_{17}BrClNO_2$	65
10	XIII	H	H	F	H	HCl	Colourless Powder	246-248	$C_{13}H_{17}ClFNO_2$	63

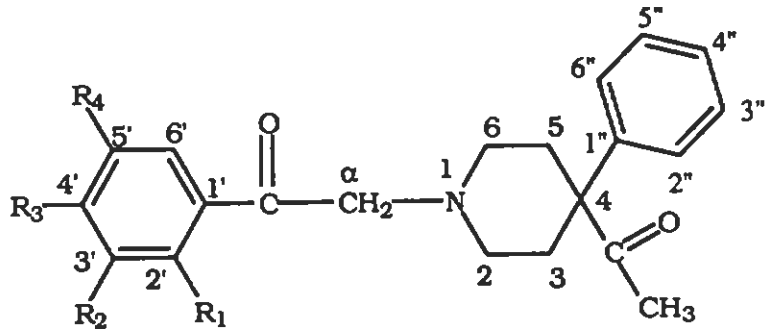
R

Table-2: Substituted Phenacyl Derivatives of 4-Hydroxy-4-Phenylpiperidine and Their Physical Data.



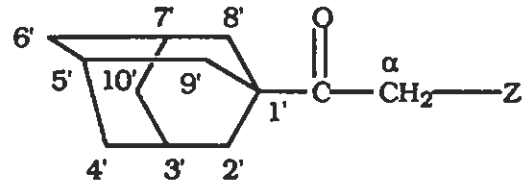
S. No.	Compund	R_1	R_2	R_3	R_4	Salt	Colouur/Shape	M.P. (°C)	Mol. Formula	Yield (%)
1	XIV	H	H	CH_3	H	HBr	Colourless Crystal	168-170	$C_{20}H_{24}BrNO_2$	69
2	XV	H	OCH_3	H	H	HBr	Brownish rods	214-216	$C_{20}H_{24}BrNO_3$	58
3	XVI	H	H	OCH_3	H	HBr	Colourless Powder	144-146	$C_{20}H_{24}BrNO_3$	63
4	XVII	OCH_3	H	OCH_3	H	HBr	Colourless Powder	176-178	$C_{21}H_{26}BrNO_4$	70
5	XVIII	OCH_3	H	H	OCH_3	HBr	Light Yellow Crystal	76-78	$C_{21}H_{26}BrNO_4$	49
6	XIX	H	OH	OH	H	HCl	Brownish Poder	230-232	$C_{19}H_{22}ClNO_4$	75
7	XX	H	H	Ph	H	HBr	Off White Solid	186-188	$C_{25}H_{26}BrNO_2$	80
8	XXI	H	H	Br	H	HBr	Colourless Needles	204-206	$C_{19}H_{21}Br_2NO_2$	67
9	XXII	H	H	Cl	H	HBr	Colourless Plates	190-192	$C_{19}H_{21}BrClNO_2$	64
10	XXIII	H	H	F	H	HCl	Colourless Crystals	198-200	$C_{19}H_{21}ClFNO_2$	54

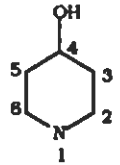
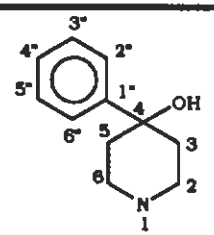
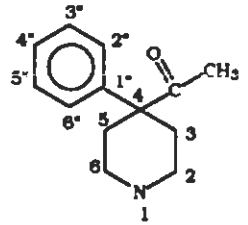
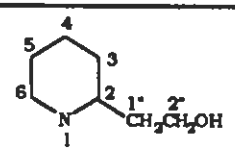
Table-3: Substituted Phenacyl Derivatives of 4-Acetyl-4-Phenylpiperidine and Their Physical Data.



S. No.	Compound	R_1	R_2	R_3	R_4	Salt	Colour/Shape	M.P. (°C)	Mol. Formula	Yield (%)
1	XXIV	H	H	CH_3	H	HBr	Colourless Crystals	226-228	$C_{22}H_{26}BrNO_2$	58
2	XXV	H	OCH_3	H	H	HBr	Colourless Needles	234-236	$C_{22}H_{26}BrNO_3$	52
3	XXVI	H	H	OCH_3	H	HBr	Off White Crystals	240-242	$C_{22}H_{26}BrNO_3$	60
4	XXVII	OCH_3	H	OCH_3	H	HBr	Dark Brown Rods	224-226	$C_{23}H_{28}BrNO_4$	67
5	XXVIII	OCH_3	H	H	OCH_3	HBr	Colourless Powder	204-206	$C_{23}H_{28}BrNO_4$	45
6	XXIX	H	OH	OH	H	HCl	Light Brown Powder	270-272	$C_{21}H_{24}ClNO_4$	71
7	XXX	H	H	Ph	H	HBr	Colourless Crystals	197-199	$C_{27}H_{28}BrNO_2$	53
8	XXXI	H	H	Br	H	HBr	Colourless Plates	238-240	$C_{21}H_{23}Br_2NO_2$	48
9	XXXII	H	H	Cl	H	HBr	Colourless Crystals	262-264	$C_{21}H_{23}BrClNO_2$	64
10	XXXIII	H	H	F	H	HCl	Colourless Needles	208-210	$C_{21}H_{23}ClFNO_2$	49

Table-4: Adamantyl Derivatives of 4-Hydroxypiperidine, 4-Hydroxy-4-phenylpiperidine, 4-Acetyl-4-Phenylpiperidine and 2-Piperidineethanol and Their Physical Data.



S. No.	Compound	Z	Salts	Colour/Shape	M.P. (°C)	Mol. Formula	Yield
1	XXXIV		HBr	Colourless Plates	264-265	$C_{17}H_{28}BrNO_2$	58
2	XXXV		HBr	Off White Powder	268-270	$C_{23}H_{32}BrNO_2$	63
3	XXXVI		HBr	Colourless Needles	238-240	$C_{25}H_{34}BrNO_2$	70
4	XXXVII		HBr	Red Gumy Matter	-	$C_{19}H_{32}BrNO_2$	65

PHARMACOLOGICAL STUDIES

ANALGESIC ACTIVITY

Analgesic activity of compounds was tested as antinociceptive effect against chemical and thermal stimuli.

Female mice of NMRI strain weighing between 18-22 gms were used in the writhing test and those for thermal test were mice of either sex weighing between 20-30 gms. (The animals were maintained under standard colony conditions i.e., 12 hrs. light and 12 hrs. dark, temperature $21 \pm 2^{o}C$, fed with balance diet and water ad libitum).

Chemical Method (Writhing Test)

A group of 5 mice were injected i.p. 0.6% acetic acid 15 minutes after administration of compound and the number of writhing movements were noted in control mice (Wc) and in the treated mice (Wx) (Bentley *et al.*, 1983).

$$\text{\% Inhibition of acetic acid Induced stretching response} = 100 - \left[\left[\frac{Wx}{Wc}\right]100\right]$$

Thermal Method (Tail Flick Test)

The procedure used was a modification of Distasi *et al.*, (1988). The basal reaction time of each mouse in a group of five was determined using the tail withdrawal response when one third of the tail was immersed in a water bath at 55^{o}C. The cut-off time for immersion was 30 seconds. The reaction time was evaluated at +30, +60, +90, +120 minutes after the administration of compound. Morphine HCl (10 mg/kg) and aspirin (300 mg/kg) were used as standard drugs in case of a control group which was always run parallel to the compound treated group.

NEUROCHEMICAL ESTIMATIONS

The reverse-phase high performance liquid chromatography (HPLC) is a simple and sensitive procedure for simultaneous determination of monoamine transmitters and related substances including precursors and metabolites (Ishikawa and Mcgaugh, 1982). This technique provides a useful tool in the assessment of neurochemical changes in brain during on-going steady-state behaviours or during the disruption of behaviour following administration of drugs (Loullis *et al.*, 1980) and was used for the determination of catecholamines and indolamines.

Animals

Male Albino mice (locally bred) weighing 25-30 g were housed individually in the same environmental conditions for about four days before experimentation.

Drugs

a) Pethidine injection.

b) (i) 4-Hydroxy-4-phenylpiperidine derivatives (**XVIII**, **XIX**, **XXII** and **XXIII**).

(ii) 4-Acetyl-4-phenylpiperidine derivatives (**XXXI**-**XXXIII** and **XXXVI**)

The synthetic compounds were dissolved in water for injection and injected into the test animals i.p. at a dose of 100 mg/kg body weight. Pethidine (25 mg/kg body weight) was used as a standard. Saline was administered to the control animals by the same route.

Extraction Procedure

Extraction medium was prepared (Haleem *et al.*, 1990) by mixing 3.4 ml perchloric acid, 0.1 gm sodium metabisulfite, ethylenediamine-tetra-acetate 0.001 gm and 0.01 gm cysteine. Volume was made upto 100 ml. Brain samples were homogenized in 5 volumes of extraction medium and centrifuged. The clear supernatant was decanted into eppendorf tubes for storage until analysis.

Animals were killed 1 hr. after the saline or test compound injection. Brains taken out within 1 minute, were stored at -70°C. Brain concentrations of 5-hydroxytryptamine (5-HT), 5-hydroxyindole acetic acid (5-HIAA), dopamine (DA), dihydroxyphenyl acetic acid (DOPAC), homovanillic acid (HVA) and noradrenaline (NA) were determined by HPLC-EC method, at 0.8 V electrode potential. A 5 U shim-pack clc ODS, 4.6 mm 1D* 15 cm separation column was used. The solvent system

was methanol (18%), octyl sodium sulphate (0.023%) and EDTA (0.0035%) in 0.1 M phosphate buffer (PH = 2.9). Samples from saline, pethidine and test compound injected animals were run in a balanced design.

Statistical Analysis

Data were analyzed by one-way ANOVA. Post hoc comparisons were done by Newman-Keuls test. Differences were considered significant when $P < 0.05$.

EFFECTS ON BLOOD PRESSURE

Wistar rats of either sex (200-250 gm) were used for the determination of effects of compounds on mean arterial blood pressure (MABP). The animals were anaesthetized with an intraperitoneal injection of thiopentone (pentothal, 70-90 mg/kg body weight). The right carotid artery was cannulated with heparinized polyethylene tubing PE-50, which was connected to a pressure transducer coupled with a Grass 7D model Polygraph. The left jugular vein was cannulated with similar tubing to facilitate the I.V. injection of the test compounds. The rats were injected with heparin (1000 μ/kg body weight) to prevent blood clotting.

After a 20 minutes period of equilibrium, the rats were injected I.V. with 0.2 ml saline (NaCl 0.9%) or with the same volume of test substance. Arterial blood pressure was allowed to return to the resting level between injections. Changes in blood pressure were recognized as the difference between the steady state values before and to the lowest readings after injection. Mean blood pressure was calculated as the diastolic blood pressure plus one third pulse width (Mcleod, 1970).

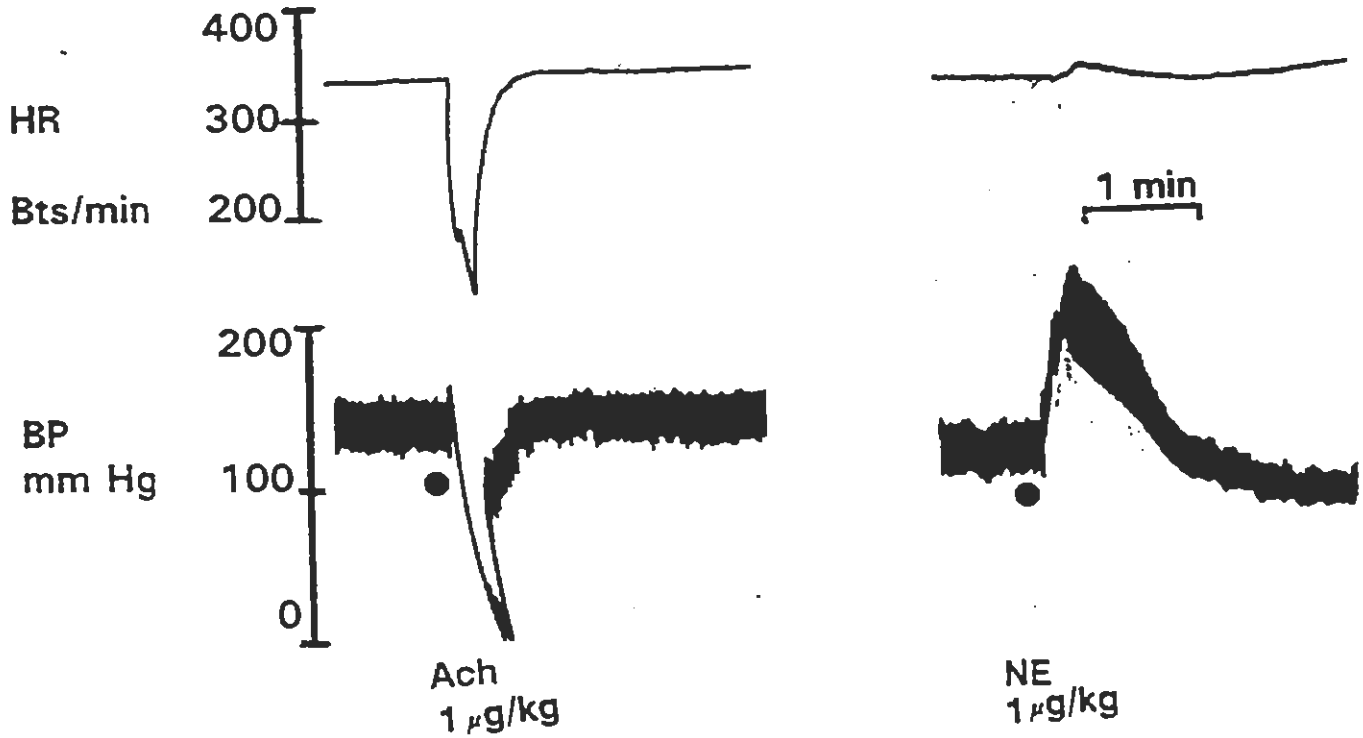


Fig. 15 Effect of Acetylcholine and Norepinephrine on blood pressure in normotensive anesthetized rats.

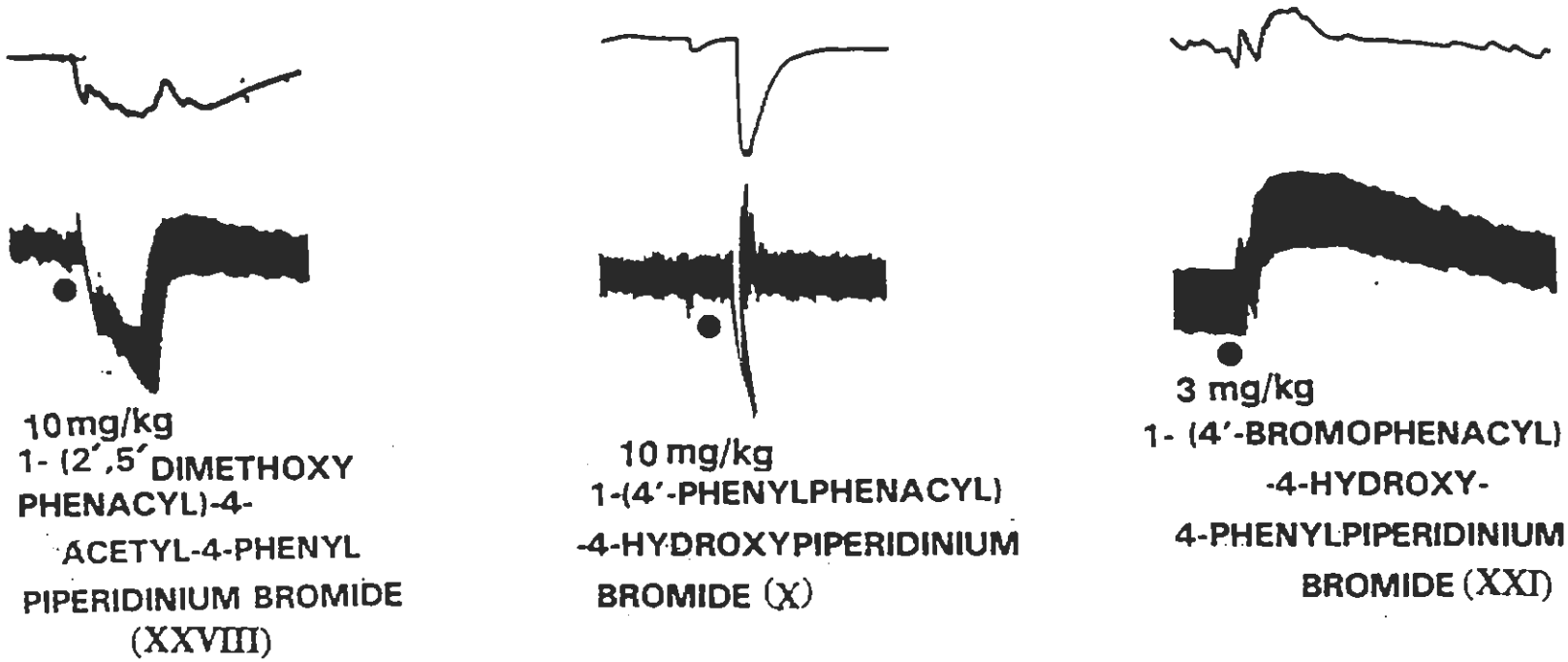


Fig. 16 Effect of piperidine derivatives on blood pressure in normotensive anesthetized rats.

EFFECTS ON SMOOTH MUSCLES CONTRACTIONS

New Zealand white rabbits (2-3 kg) of either sex starved for 24 hrs. were killed by cervical dislocation and exsanguinated. Segments of jejunum about 2 cm long were mounted in a 20 ml tissue bath containing Kreb's-Henseleit solution, maintained at 37°C and bubbled with a gas mixture of 95% O_2 and 5% CO_2. A preload of 1.0 g was applied and spontaneous contractions were recorded isotonically via a T-3 isotonic transducer on a Bioscience MD recorder. The tissues were allowed to equilibrate for 1 hr. before addition of any test compound (Gilani *et al.*, 1994).

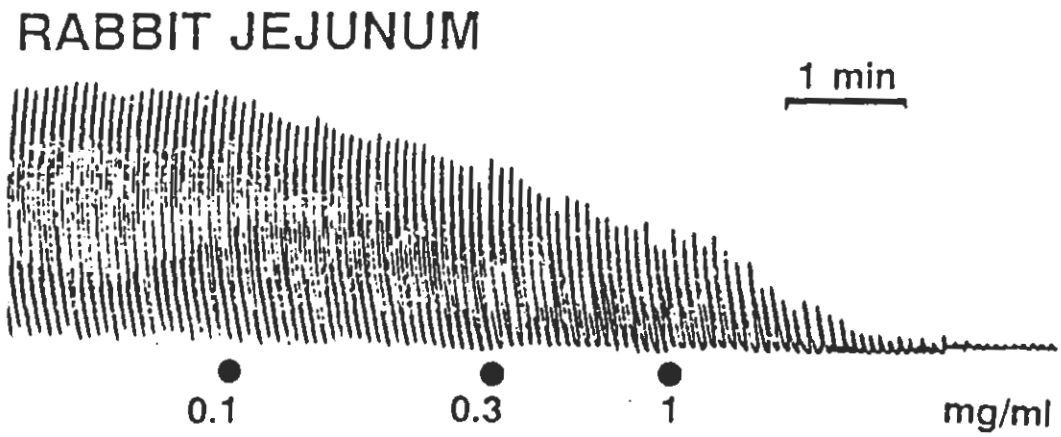


Fig. 17. Representative tracing showing inhibitory effect of test compound on spontaneous contractions of rabbit jejunum.

RESULTS

ANALGESIC ACTIVITY

The results of antinociceptive activity of substituted *N*-phenacyl derivatives of 4-hydroxypiperidine, 4-hydroxy-4-phenylpiperidine and 4-acetyl-4-phenylpiperidine (**IV-XXXIII**) along with their parent compounds (**I-III**) are presented in Table- 5-7. Table 8 presents the writhing test results of analgesic activity of adamantyl derivatives of 4-hydroxypiperidine, 4-hydroxy-4-phenylpiperidine, 4-acetyl-4-phenylpiperidine and 2-piperidineethanol (**XXXIV-XXXVII**).

Compound **I** is the starting material of substituted phenaycl derivatives of 4-hydroxypiperidine and found devoid of analgesic activity at tested doses when screened by writhing test as well as tail flick test.

Among the compounds of this series (**VI-XIII**), *para* halogenated derivatives (**XI-XIII**) exhibited maximum percent inhibition of writhing at 25-100 mg/kg doses. Compounds with chloro and fluoro substituents showed almost same level of protection against acetic acid induced writhing. Similarly

Compound **III** is the starting material of newly synthesized derivatives and showed 78, 62 and 45% inhibition of writhing causing tremors and convulsions during screening at the dose of 12.5, 25 and 50 mg/kg body weight respectively and was lethal at 100 mg/kg dose. All the compounds except one (**XXVII**) showed analgesic activity when tested by writhing test. Maximum percent inhibition of writhing was displayed by compounds (**XXVIII-XXXIII**) at the dose of 50 and 100 mg/kg body weight. The level of activity was maximum in case of compounds having halogen substituents at the benzene ring of phenacyl moiety.

All the three halogenated derivatives with Br, Cl and F at *para* position displayed almost same percent inhibition of writhing at tested doses. Amongst the methoxy substituted derivatives, compound **XXVIII** exhibited significant activity while, rest of these were slightly active except one (**XXVII**) which was altogether devoid of analgesic activity at tested doses. The compound **XXIV** with CH_3 at *para* position and compound **XXIX** having dihydroxyl group at *meta* and *para* positions, displayed almost same level of percent inhibition of writhing at both 50 and 100 mg/kg body weight.

From Table-8, it is evident that among the adamantyl derivatives, the most active compound (**XXXVI**), showed 88, 41 and 29% protection against acetic acid induced writhing at 25,

50 and 100 mg/kg doses respectively. Compound **XXXIV** and **XXXV** demonstrated almost same level of activity and compound **XXXVII** was the least active among all these four derivatives. It showed no activity at the dose of 50 mg/kg and 45% inhibition of writhing at 100 mg/kg body weight.

All the compounds (**I-XXXVII**) were also evaluated for analgesic activity by tail flick test. None of these proved active by this method.

Table-5: Results of Analgesic Activity of 4-Hydroxypiperidine HCl (I) and its Derivatives (IV-XIII).

S.No.	Compound	Dose (mg/kg)	Mean Writhing ± S.E.M.	Percent Inhibition
1	Control (Acetic acid, 0.6%)	15 ml/kg	8.50±0.35	-
2	I*	50 100	Inactive Inactive	- -
3	IV	50 100	Inactive Inactive	- -
4	V	50 100	Inactive Inactive	- -
5	VI	50 100	5.40±0.24 4.40±0.24	36 48
6	VII	50 100	Inactive 4.60±0.39	- 45
7	VIII	50 100	Inactive Inactive	- -
8	IX	50 100	Inactive Inactive	- -
9	X	50 100	Inactive 4.40±0.24	- 48
10	XI	50 100	6.00±0.31 4.60±0.24	33 49
11	XII	50 100	4.40±0.24 3.20±0.20	48 65
12	XIII	50 100	6.10±0.30 2.45±0.24	38 70
13	Aspirin	300	1.30±0.53	77
14	Morphine HCl	10	0	100

*4-Hydroxypiperidine HCl.

Table-6: Results of Analgesic Activity of 4-Hydroxy-4-Phenylpiperidine HCl (**II**) and its Derivatives (**XIV-XXIII**).

S. No	Compound	Dose (mg/kg)	Mean Writhing ± S.E.M.	Percent Inhibition
1	Control (Acetic acid, 0.6%)	15 ml/kg	8.50 ± 0.35	-
2	II*	50 100	- -	- -
3	XIV	50 100	- -	- -
4	XV	50 100	- -	- -
5	XVI	50 100	- 6.60 ± 0.24	- 27
6	XVII	50 100	- -	- -
7	XVIII	50 100	- 4.40 ± 0.24	- 48
8	XIX	50 100	6.00 ± 0.31 3.20 ± 0.20	33 65
9	XX	50 100	- 7.00 ± 0.31	- 22
10	XXI	50 100	- 6.00 ± 0.31	- 33
11	XXII	50 100	4.60 ± 0.24 2.40 ± 0.24	49 73
12	XXIII	50 100	6.00 ± 0.31 4.20 ± 0.24	29 50
13	Aspirin	300	1.30 ± 0.53	77
14	Morphine HCl	10	0	100

*4-Hydroxy-4-Phenylpiperidine HCl

Table-7: Results of Analgesic Activity of 4-Acetyl-4-Phenylpiperidine HCl (**III**) and its Derivatives (**XXIV-XXXIII**).

S.No.	Compound	Dose (mg/kg)	Mean Writhing ± S.E.M.	Percent Inhibition
1	Control (Acetic acid, 0.6%)	15 ml/kg	8.50±0.35	-
2	**III***	12.5	2.40±0.20	78
		25	2.80±0.22	62
		50	4.80±0.24	45
3	**XXIV**	50	4.20±0.37	50
		100	2.80±0.20	67
4	**XXV**	50	-	-
		100	4.80±0.20	42
5	**XXVI**	50	-	-
		100	5.80±0.20	31
6	**XXVII**	50	-	-
		100	-	-
7	**XXVIII**	50	4.00±0.30	52
		100	2.40±0.24	71
8	**XXIX**	50	6.00±0.30	29
		100	2.80±0.20	67
9	**XXX**	50	4.60±0.37	45
		100	2.60±0.40	69
10	**XXXI**	50	5.20±0.37	38
		100	1.20±0.20	86
11	**XXXII**	50	4.80±0.37	43
		100	2.40±0.24	71
12	**XXXIII**	50	4.80±0.37	42
		100	1.60±0.24	81
13	Aspirin	300	1.30±0.53	77
14	Morphine HCl	10	0	100

*4-Acetyl-4-phenylpiperidine HCl.

Table-8: Results of Analgesic Activity of Adamantyl Derivatives of 4-Hydroxypiperidine, 4-Hydroxy-4-Phenylpiperidine, 4-Acetyl-4-Phenylpiperidine and 2-Piperidine-ethanol (**XXXIV-XXXVII**).

S.No.	Compound	Dose (mg/kg)	Mean Writhing ± S.E.M.	Percent Inhibition
1	Control (Acetic acid, 0.6%)	15 ml/kg	8.50±0.35	-
2	**XXXIV**	50	6.60±0.51	22
		100	3.60±0.40	57
3	**XXXV**	50	4.00±0.54	57
		100	6.20±0.20	23
4	**XXXVI**	25	0.80±0.20	88
		50	5.00±0.31	41
		100	6.40±0.40	29
5	**XXXVII**	50	Inactive	-
		100	4.60±0.39	45
6	Aspirin	300	1.30±0.53	77
7	Morphine HCl	10	0	100

NEUROCHEMICAL ESTIMATIONS

Results of effects of four substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines (**XVIII**, **XIX**, **XXII** and **XXIII**) on mice brain monoamines levels, depicted in Fig. 4-9 are discussed as under.

Fig. 4 shows that administration of pethidine as well as synthetic compounds **XIX** and **XXII** did not alter 5-HT levels in brain. Compound **XXIII** increased brain 5-HT levels significantly as compared to saline injected mice. The levels of 5-HT were decreased significantly by compound **XVIII** as compared to pethidine injected mice.

Fig. 5 shows that pethidine, compound **XVIII** and **XIX** did not change the levels of 5-HIAA as compared to control, whereas, administration of compounds **XXII** and **XXIII** increased 5-HIAA levels significantly.

Fig. 6 indicates that pethidine and all the four synthetic compounds understudy decreased dopamine levels in brain. The decrease produced by compound **XXII** was greater than

that of pethidine. While an equivalent decrease was observed on administering pethidine and compounds **XVIII**, **XIX** and **XXIII**.

Fig. 7 depicts that unlike DA, the concentrations of DOPAC in brain were not affected by the administration of pethidine as well as compounds **XVIII**, **XIX** and **XXII**. However, injection of compound **XXIII** caused significant increase in DOPAC brain concentrations.

Fig. 8 shows that administration of compound **XXII** and **XXIII** significantly increased brain HVA levels in comparison with control and pethidine treated mice. Rest of the compounds did not alter HVA levels.

Fig. 9 reveals that administration of compounds **XIX**, **XXII**, **XXIII** and pethidine enhanced concentrations of noradrenaline in the brain. Pethidine and compounds **XIX** and **XXIII** manifested almost same level of enhancement. Conversely, the administration of compound **XVIII** caused considerable decrease in brain noradrenaline levels.

The results of effects of 4-acetyl-4-phenylpiperidine derivatives (**XXX-XXXI and XXXVI**) on mice brain 5-HT, 5-HIAA, DA, DOPAC and HVA levels, presented in Fig. 10-14 are as under:

Fig. 10 reveals that the effects of 4-acetyl-4-phenylpiperidine derivatives on brain 5-HT levels were not so promising. Only compound **XXXII** decreased 5-HT levels significantly as compared to control and untreated group. Rest of the compounds did not cause significant change in 5-HT levels in mice brain.

Fig. 11 presents the pattern of effects produced by this series of compounds on brain 5-HIAA levels which was different as compared to that of 4-hydroxy-4-phenylpiperidine derivatives. Compound **XXXI** and **XXXII** enhanced the 5-HIAA levels, while compounds **XXXIII** and **XXXVI** remarkably decreased 5-HIAA levels in mice brain as compared to control and untreated group .

Fig. 12 relates that the compounds did not change the dopamine concentrations in mice brain. Only compound **XXXII**

lowered the DA levels but insignificantly as compared to control and untreated group.

Fig. 13 depicts that like dopamine, no significant effects on brain DOPAC levels were produced upon administering compounds **XXXI-XXXIII**. Only compound **XXXVI** significantly increased brain DOPAC concentrations as compared to control and untreated group.

Fig. 14 presents that all the four compounds triggered HVA concentration in brain when compared to control as well as untreated group. The enhancement in mice brain HVA levels caused by compounds **XXXI-XXXIII** was almost same. Compound **XXXVI** was slightly lesser active than compounds **XXXI-XXXIII** in increasing HVA levels in mice brain.

Fig. 1

Standard chromatogram of NA, DOPAC, DA, 5-HIAA, HVA and 5-HT.

S. No.	Name	Time	Peak area	Concentration (ng/ml)
1.	NA	3.95	157630	82
2.	DOPAC	5.09	218828	100
3.	DA	5.34	328415	81
4.	5-HIAA	6.64	585138	100
5.	HVA	8.49	315186	100
6.	5-HT	9.14	357926	86

Fig. 2a

Chromatogram of brain extract of control mice injected with saline showing the separation of NA, DOPAC, DA, 5-HIAA, HVA and 5-HT.

S. No.	Name	Time	Peak area	Concentration (ng/ml)
1.	NA	4.05	80934	312.00
2.	DOPAC	5.16	30785	49.24
3.	DA	5.78	60345	265.38
4.	5-HIAA	6.93	48392	129.60
5.	HVA	8.65	35071	64.00
6.	5-HT	9.97	93201	352.24

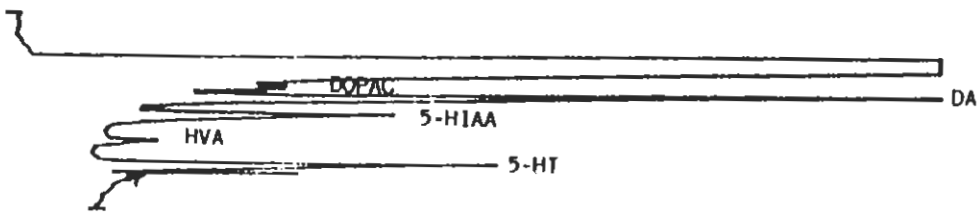


Fig. 2b

Chromatogram of brain extract of control mice injected with saline showing the separation of DOPAC, DA, 5-HIAA, HVA and 5-HT.

S. No.	Name	Time	Peak area	Concentration (ng/ml)
1.	DOPAC	5.03	21564	34.17
2.	DA	5.57	540983	574.21
3.	5-HIAA	6.60	142930	109.06
4.	HVA	8.33	38054	59.22
5.	5-HT	9.97	378693	592.50

Fig. 3a

Chromatogram of brain extract of mice injected with test compound showing the separation of NA, DOPAC, DA, 5-HIAA, HVA and 5-HT.

S. No.	Name	Time	Peak area	Concentration (ng/ml)
1.	NA	4.04	73821	298.40
2.	DOPAC	5.16	40789	53.76
3.	DA	5.69	40385	162.99
4.	5-HIAA	6.78	48250	168.30
5.	HVA	8.50	23454	46.32
6.	5-HT	10.10	355324	580.39

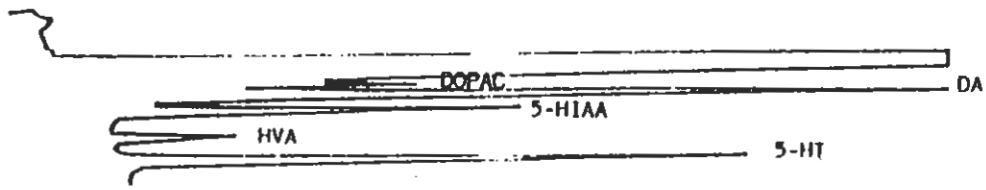


Fig. 3b

Chromatogram of brain extract of mice injected with test compound showing the separation of DOPAC, DA, 5-HIAA, HVA and 5-HT.

S. No.	Name	Time	Peak area	Concentration (ng/ml)
1.	DOPAC	4.99	53089	89.83
2.	DA	5.53	744900	84.23
3.	5-HIAA	6.48	105474	85.93
4.	HVA	8.18	65556	109.06
5.	5-HT	9.75	355334	593.66

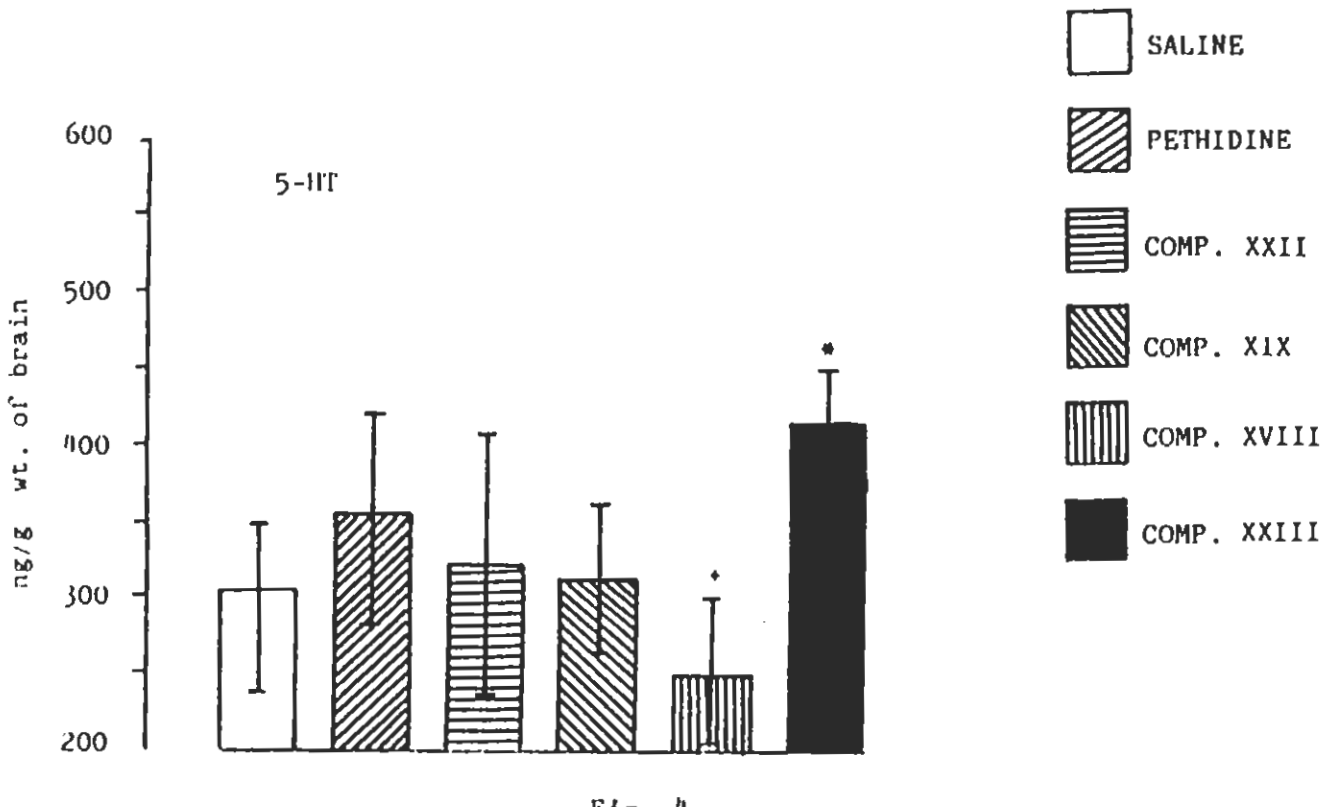


Fig. 4

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain 5-HT levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test : * $P < 0.05$ from control and +$P < 0.05$ from pethidine treated mice following one-way ANOVA ($F = 5.91$ df 1,36 $P < 0.05$).

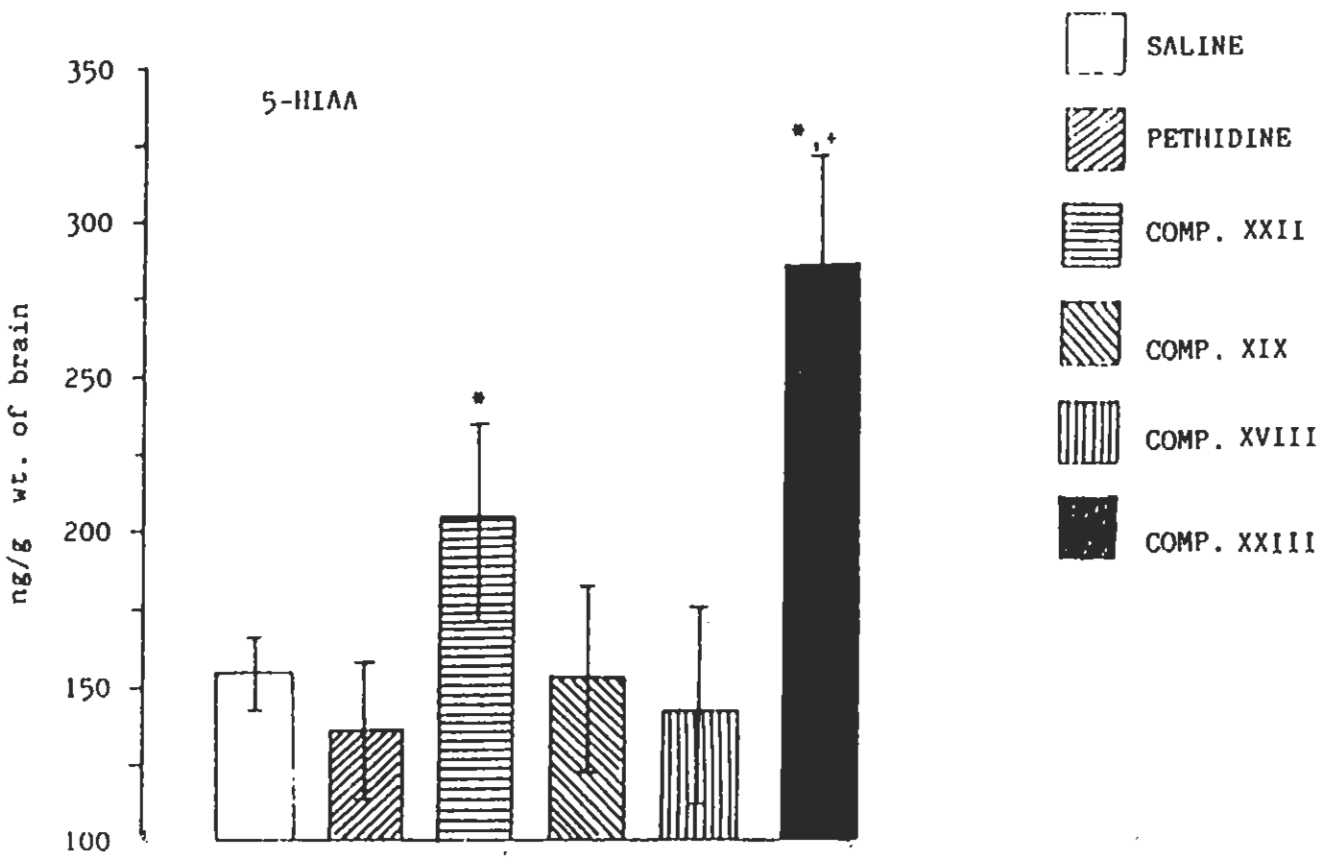


Fig. 5

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain 5-HIAA levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test : * P < 0.01 from control and +P < 0.01 from pethidine treated mice following one-way ANOVA (F = 28.60 df 1,36 P < 0.01).

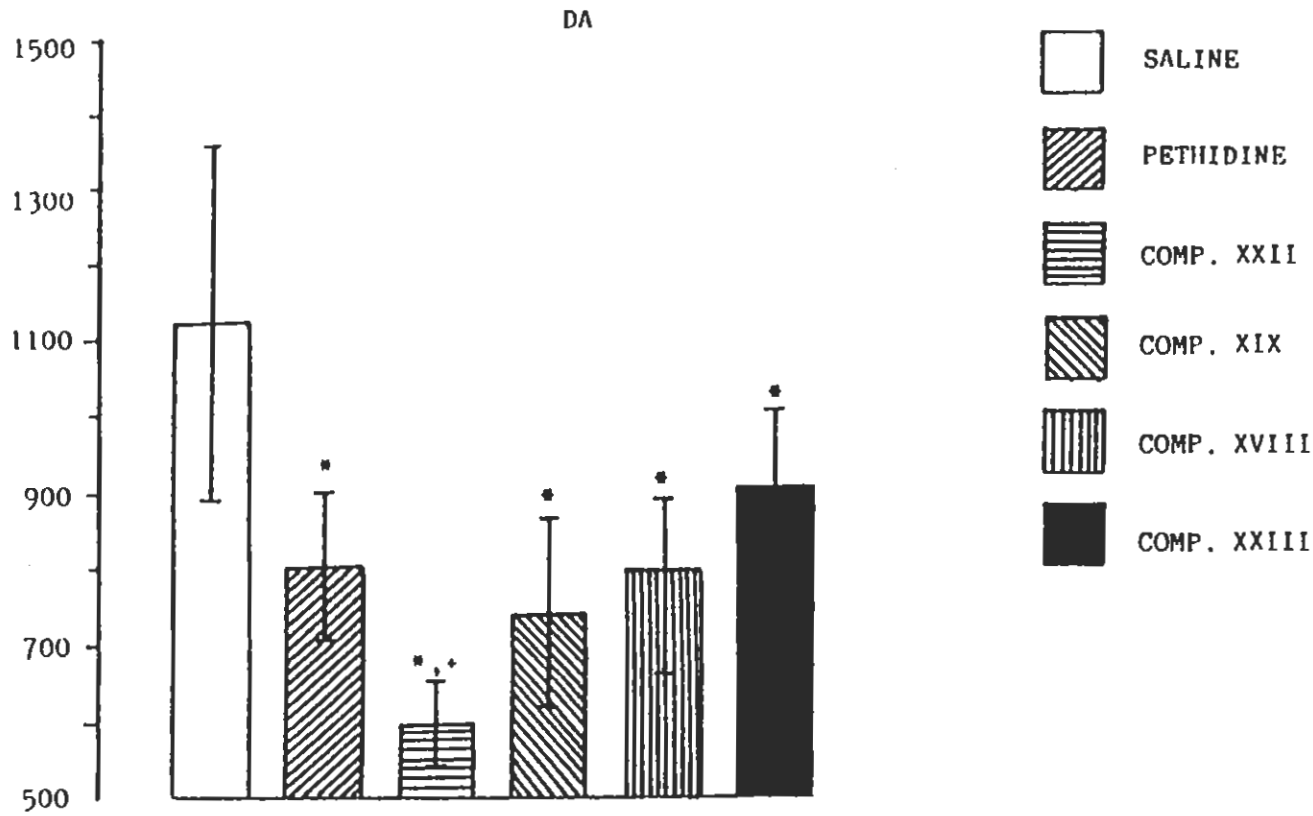


Fig. 6

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain DA levels. Values are means ±S.D. (n=7). Significant differences by Newman Keuls test : * P < 0.01 from control and +P < 0.05 from pethidine treated mice following one-way ANOVA (F = 131 df 1,36 P < 0.01).

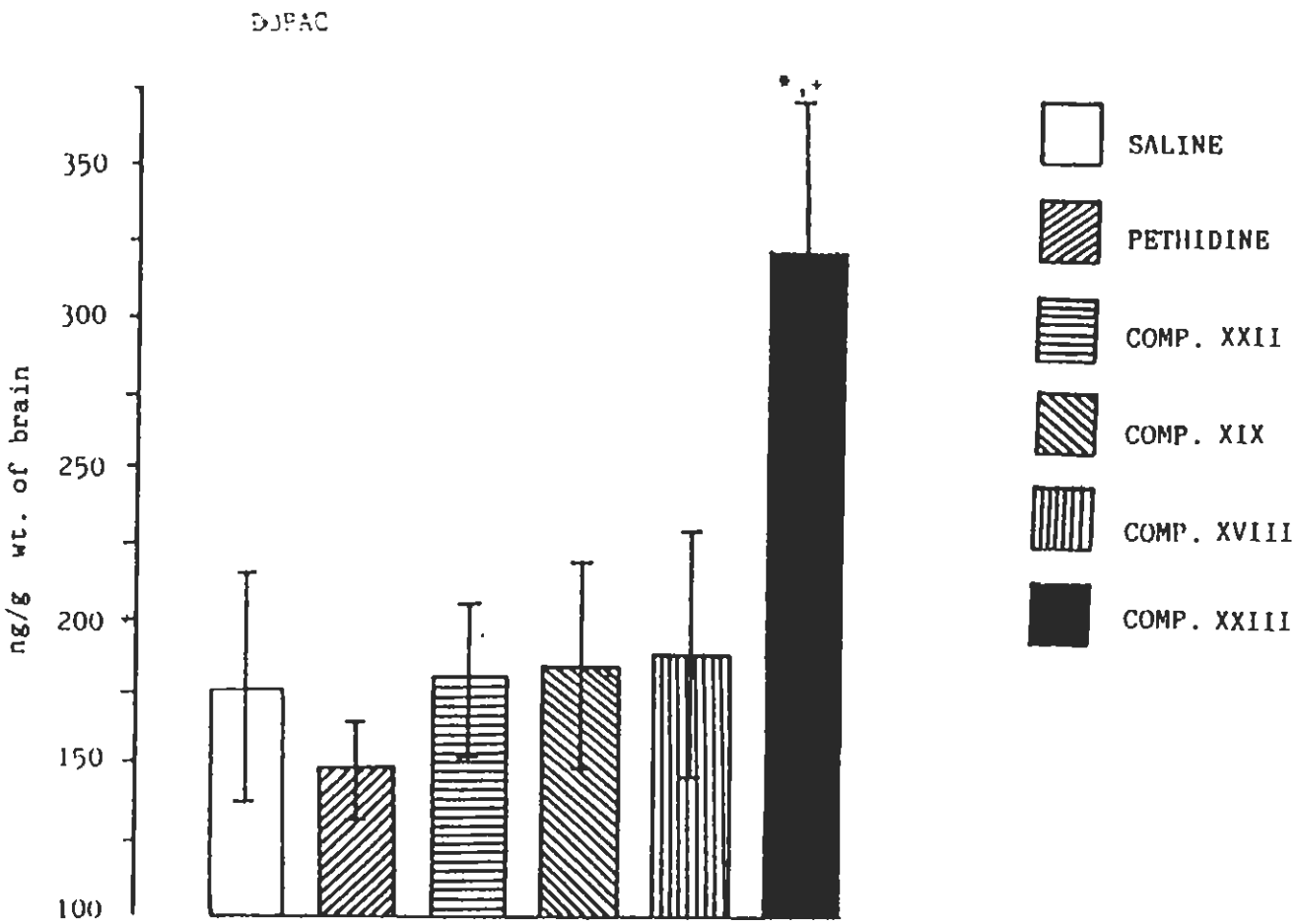


Fig. 7

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain DOPAC levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test : * $P < 0.01$ from control and +$P < 0.01$ from pethidine treated mice following one-way ANOVA ($F = 21.25$ df 1,36 $P < 0.01$).

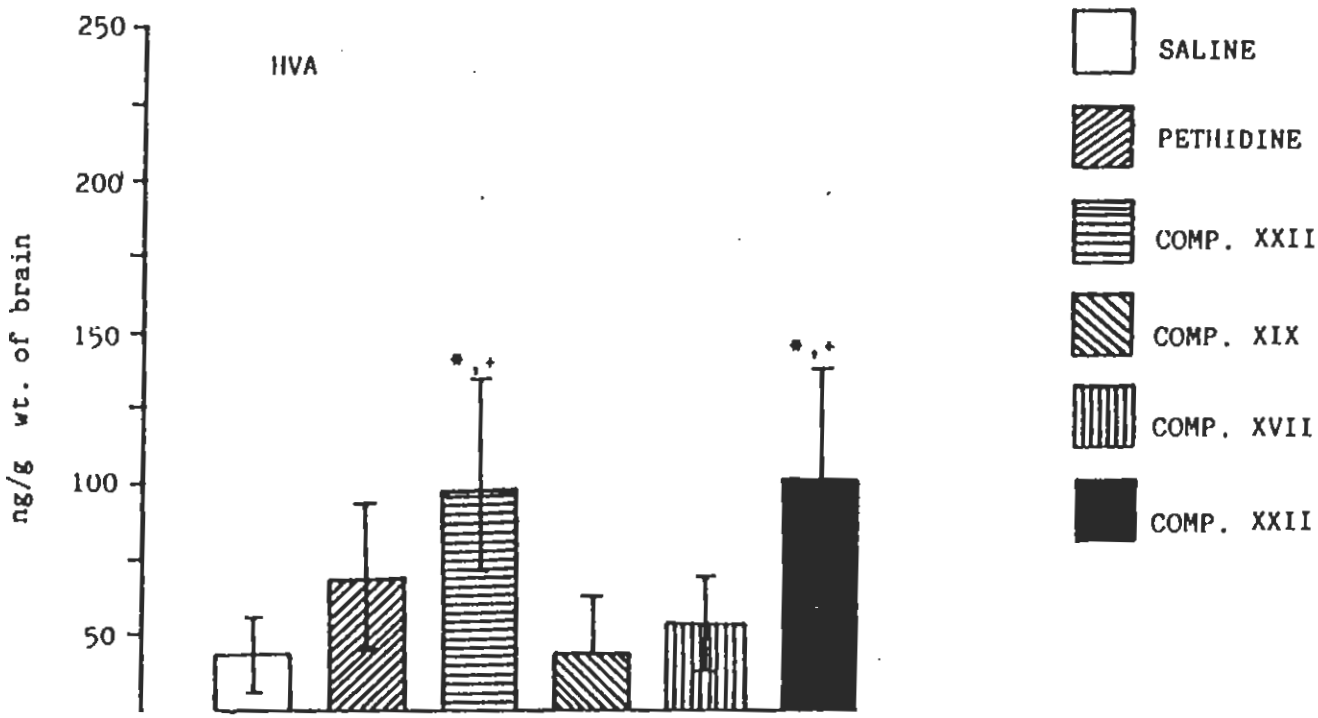


Fig. 8

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain HVA levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test : * $P < 0.01$ from control and +$P < 0.05$ from pethidine treated mice following one-way ANOVA ($F = 7.97$ df 1,36 $P < 0.01$).

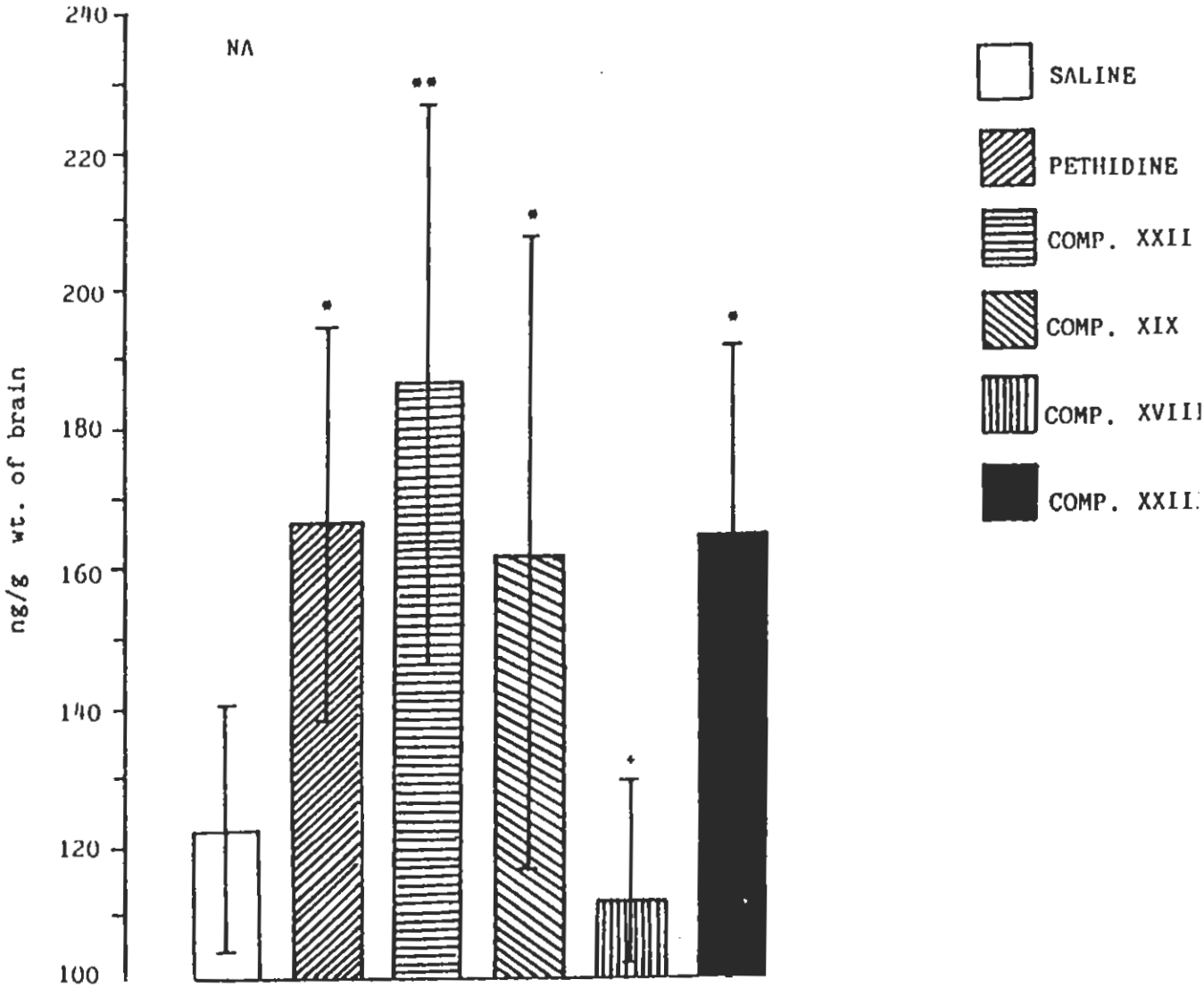


Fig. 9

The effects of pethidine and substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines on brain NA levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test : ** P < 0.01, *P < 0.05 from control and +P < 0.05 from pethidine treated mice following one-way ANOVA (F = 5.89 df 1,36 P < 0.05).

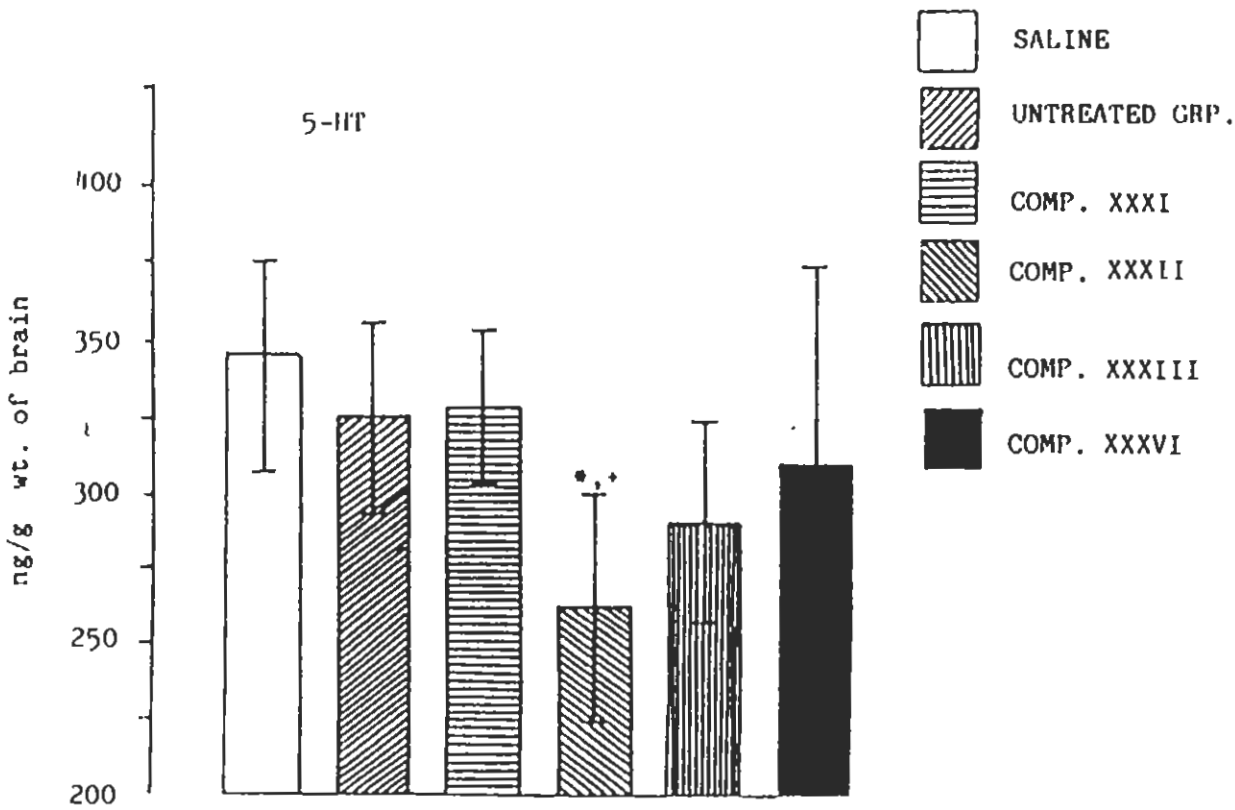


Fig. 10

The effects of 4-acetyl-4-phenylpiperidine derivatives on brain 5-HT levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test: * P < 0.01 from control and +P < 0.05 from untreated group following one-way ANOVA (F = 3.94, df 1,36 P < 0.01).

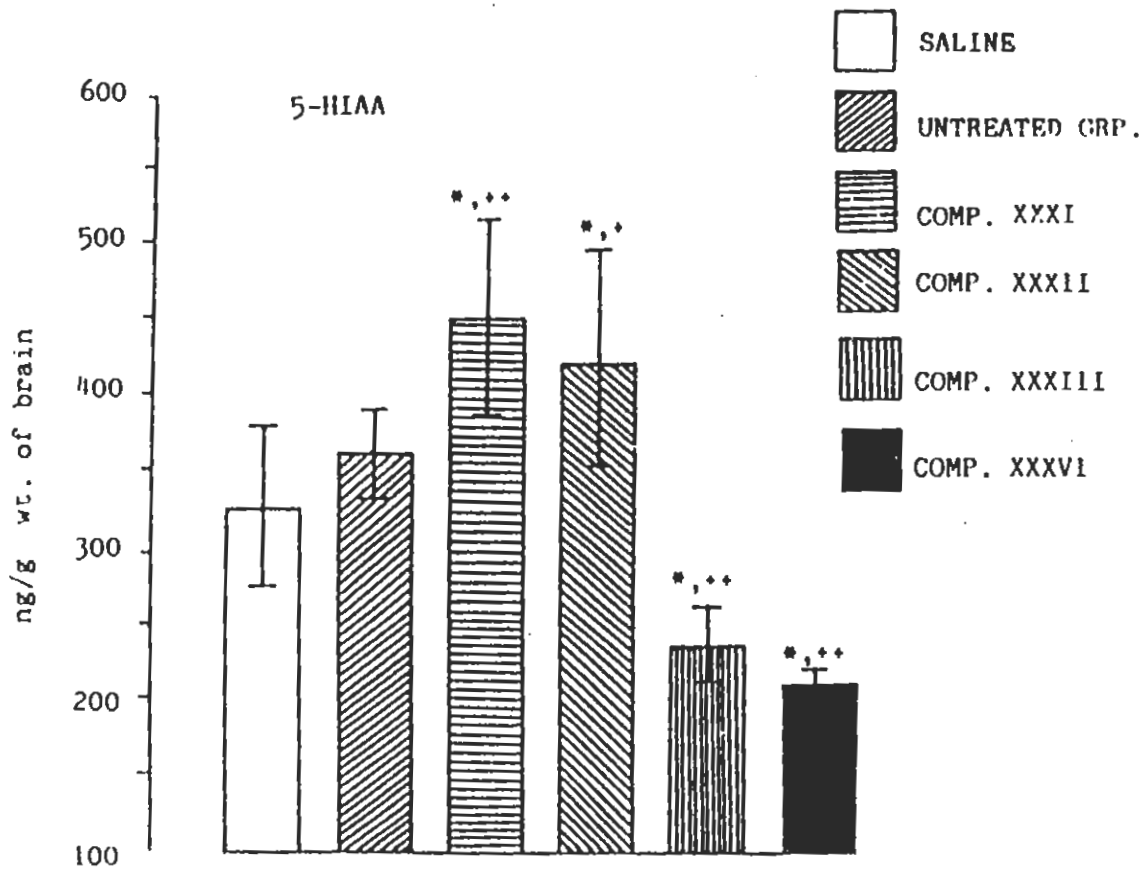


Fig. 11

The effects of 4-acetyl-4-phenylpiperidine derivatives on brain 5-HIAA levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test: * $P < 0.01$ from control and +$P < 0.05$, ++$P < 0.01$ from untreated group following one-way ANOVA ($F = 28.79$, df 1,36 $P < 0.01$).

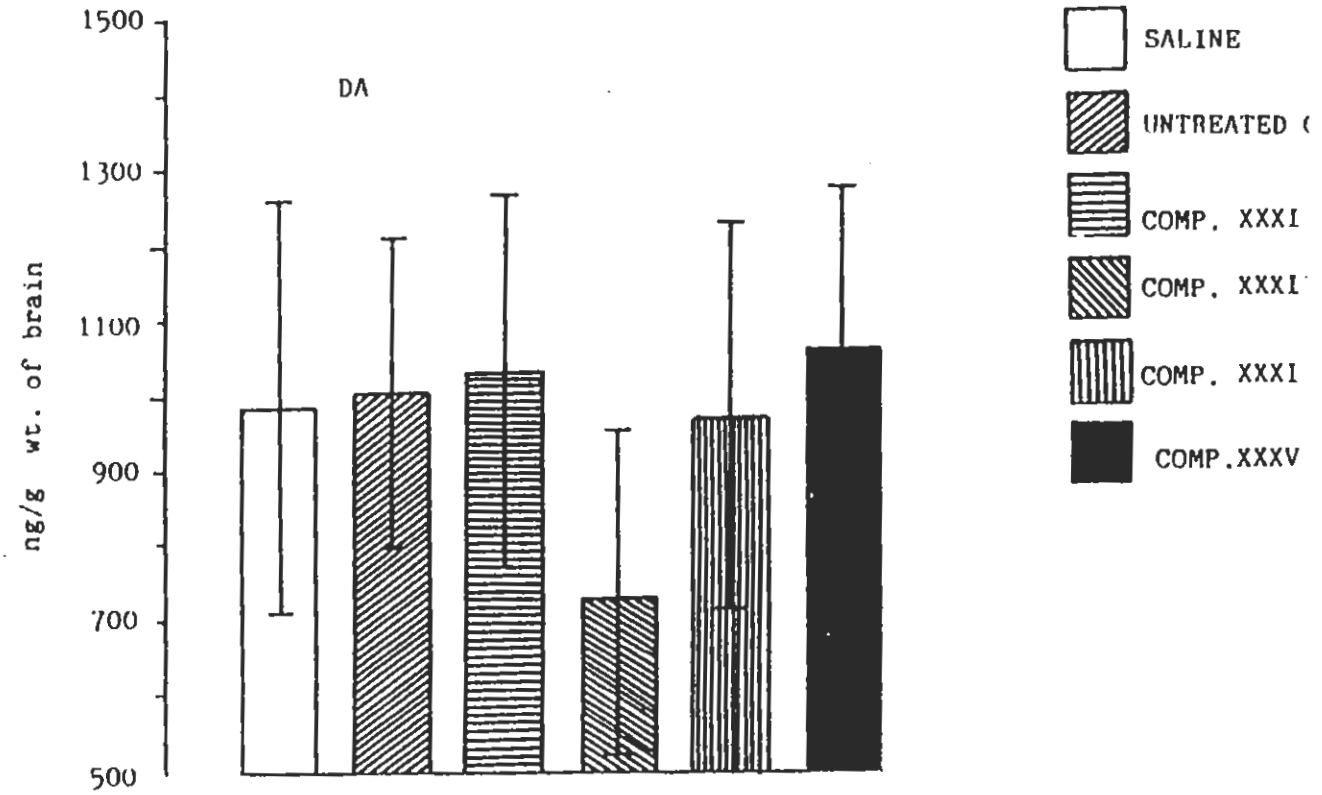


Fig. 12

The effects of 4-acetyl-4-phenylpiperidine derivatives on brain DA levels. Values are means ± S.D. (n=7). Differences were not significant following one-way ANOVA (F = 1.68, df 1,36 (n.s).

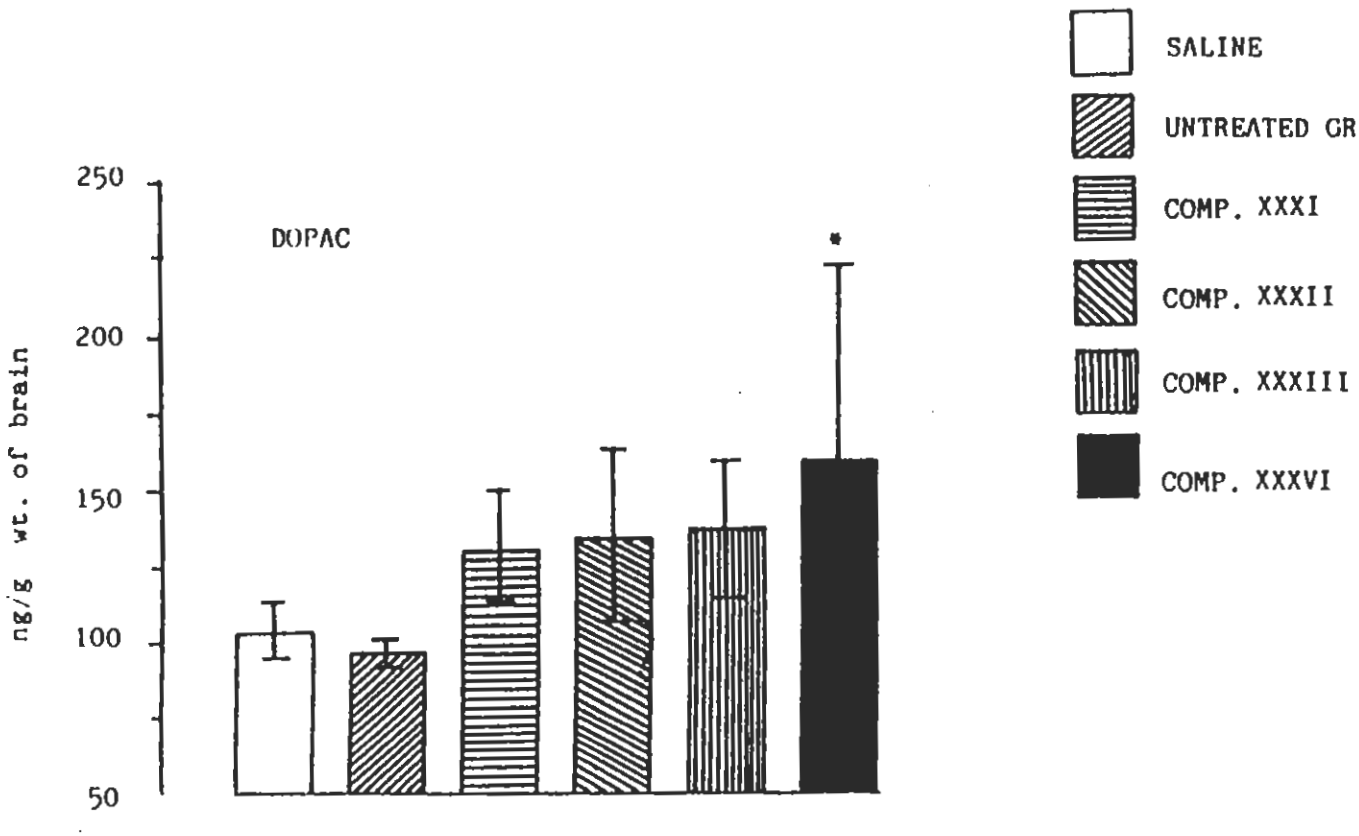


Fig. 13

The effects of 4-acetyl-4-phenylpiperidine derivatives on brain DOPAC levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test: * $P < 0.05$ from control following one-way ANOVA ($F = 3.87$, df 1,36 $P < 0.05$).

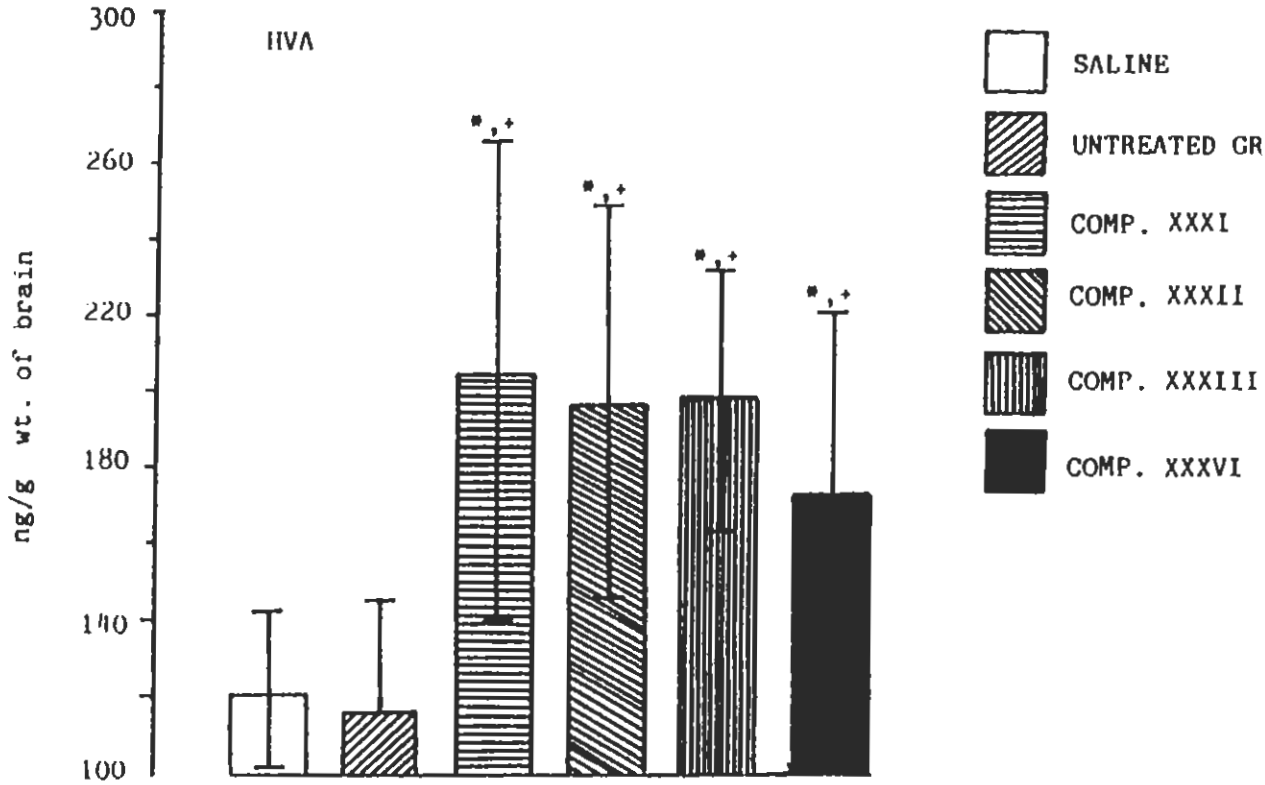


Fig. 14

The effects of 4-acetyl-4-phenylpiperidine derivatives on brain HVA levels. Values are means ± S.D. (n=7). Significant differences by Newman Keuls test:* P < 0.01 from control and +P < 0.01 from untreated group following one-way ANOVA (F = 6.00, df 1,36 P < 0.01).

EFFECTS ON BLOOD PRESSURE

The results concerning effects of piperidine derivatives (**IV-XXXIII**) along with their parent compounds (**I-III**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats are presented in Table 9-11 and described as under:

Table-9 presents the effects of 4-hydroxypiperidine (**I**) and its derivatives (**IV-XIII**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats.

i) Compound **I** is the starting material of all the derivatives and gave triphasic response at the dose of 30 mg/kg body weight.

ii) Compound **IV** and **XIII** showed hypotensive activity at the dose of 20 and 10 mg/kg respectively.

iii) Only one compound (**VI**) demonstrated hypertensive response at the dose of 20 mg/kg.

iv) Two compounds (**X** and **XI**) exhibited biphasic response (hypotensive followed by hypertensive) at the dose of 10 mg/kg.

v) Like starting material, compound **XII** also gave triphasic response but at lower dose, i.e. 10 mg/kg.

vi) Rest of the compounds (**V**, **VII**, **VIII**, **IX**) were devoid of any effect on mean arterial blood pressure upto the dose of 30 mg/kg.

Table-10 reveals the effects of 4-hydroxy-4-phenylpiperidine HCl (**II**) and its derivatives (**XIV-XXIII**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats.

i) Compound **II** is the starting material of all the derivatives presented in Table-10 and gave dual response at two different doses. It displayed hypertensive activity upon administering at the dose of 10 mg/kg whereas, it became hypotensive when the dose was increased to 30 mg/kg.

ii) Three derivatives (**XVII**, **XIX** and **XXIII**) showed hypotensive activity with **XVII** being more potent. The compound **XVII** caused almost similar fall in blood pressure (84%) at the dose of 3 mg/kg to that observed with 10 mg/kg of **XIX** (88%) or **XXIII** (89%).

iii) Rest of the compounds (**XIV**, **XV**, **XVI**, **XVIII**, **XXI** and **XXII**) except one (**XX**) exhibited hypertensive activity. All hypertensive compounds except one (**XXI**) were effective at the dose of 10 mg/kg, while **XXI** showed activity (89%) at lower dose (3 mg/kg).

iv) Only one compound (**XX**) was found to be inactive upto the dose of 30 mg/kg.

Table-11 depicts the effects of 4-acetyl-4-phenylpiperidine HCl (**III**) and its derivatives (**XXIV-XXXIII**) on mean arterial blood pressure (MABP) in normotensive anaesthetized rats. The results are as under:

i) Compound **III** is the precursor of all these derivatives and showed hypotensive effect at the dose of 10 mg/kg .

ii) Six compounds (**XXIV**, **XXVII**, **XXVIII** and **XXXI-XXXIII**) demonstrated hypotensive response. The compound **XXIV** caused 62% reduction in blood pressure at the dose of 3 mg/kg while, compounds **XXVII** and **XXVIII** showed similar hypotensive response (79 and 83% respectively) at 10 mg/kg. The remaining three compounds (**XXXI-XXXIII**) caused hypotensive responses of the magnitude

of 88, 83 and 39% respectively at the same dose of 3 mg/kg.

iii) Only two compounds (**XXVI** and **XXIX**) showed hypertensive response at the doses of 3 and 10 mg/kg respectively.

iv) Among the derivatives, **XXV** was the only one which showed biphasic (hypotensive followed by hypertensive) response at 10 mg/kg and **XXX** was the sole inactive derivative upto the dose as high as 30 mg/kg.

Table-9: Effects of 4-Hydroxypiperidine HCl (I) and its Derivatives (IV-XIII) on Mean Arterial Blood Pressure (MABP) in Normotensive Anaesthetized Rats.

S.No.	Compound	Dose (mg/kg)	Response	% Change in blood pressure (mm Hg)
1	I*	30	Triphasic	-
2	IV	20	Hypotensive	-46.3
3	V	30	Inactive	-
4	VI	20	Hypertensive	+39.8
5	VII	30	Inactive	-
6	VIII	30	Inactive	-
7	IX	30	Inactive	-
8	X	10	Biphasic	-62, +22
9	XI	10	Biphasic	-40, +24
10	XII	10	Triphasic	-
11	XIII	10	Hypotensive	-82.2

*4-Hydroxypiperidine HCl

Table-10: Effects of 4-Hydroxy-4-Phenylpiperidine HCl (II) and its Derivatives (XIV-XXIII) on Mean Arterial Blood Pressure (MABP) in Normotensive Anaesthetized Rats.

S.No.	Compound	Dose (mg/kg)	Response	% Change in blood pressure (mm Hg)
1	II*	10	Hypertensive	+8
2	II*	30	Hypotensive	-28
3	XIV	10	Hypertensive	+57
4	XV	10	Hypertensive	+36
5	XVI	10	Hypertensive	+65
6	XVII	3	Hypotensive	-84
7	XVIII	10	Hypertensive	+56
8	XIX	10	Hypotensive	-88
9	XX	30	Inactive	-
10	XXI	3	Hypertensive	+89
11	XXII	10	Hypertensive	+28
12	XXIII	10	Hypotensive	-89

*4-Hydroxy-4-phenylpiperidine HCl

Table-11: Effects of 4-Acetyl-4-Phenylpiperidine HCl (**III**) and its Derivatives (**XXIV-XXXIII**) on Mean Arterial Blood Pressure (MABP) in Normotensive Anaesthetized Rats.

S.No.	Compound	Dose (mg/kg)	Response	% Change in blood pressure (mm Hg)
1	III*	10	Hypotensive	-34
2	XXIV	3	Hypotensive	-62
3	XXV	10	Biphasic	-59, +21
4	XXVI	3	Hypertensive	+24
5	XXVII	10	Hypotensive	-79
6	XXVIII	10	Hypotensive	-83
7	XXIX	10	Hypertensive	+18
8	XXX	30	Inactive	-
9	XXXI	3	Hypotensive	-88
10	XXXII	3	Hypotensive	-83
11	XXXIII	3	Hypotensive	-39

*4-Acetyl-4-Phenylpiperidine HCl

EFFECTS ON SMOOTH MUSCLES CONTRACTIONS

Substituted phenacyl derivatives of 4-hydroxypiperidine, 4-hydroxy-4-phenylpiperidine and 4-acetyl-4-phenylpiperidine (**IV-XXXIII**) were also studied for their effects on spontaneous contractions of isolated rabbit jejunum. Results are presented in Table 12.

All the derivatives except three (**VIII**, **IX** and **XXX**) caused relaxant effect on spontaneous contraction of rabbit jejunum at the dose range of 0.1-2 mg/ml whereas, these three derivatives were found inactive upto the dose of 2 mg/ml.

Among the twenty seven active compounds, eight (**X**, **XV**, **XXII-XIV** and **XXVI-XXVIII**) showed relaxant effect at the dose of 0.1 mg/ml, eleven (**IV-VI**, **XII-XIV**, **XVII**, **XXV** and **XXXI-XXXIII**) at 0.3 mg/ml, four (**XVI**, **XX**, **XXI** and **XXIX**) at 0.5 mg/ml, two (**XVIII** and **XIX**) at 0.7 and one each (**VII** and **XI**) at 1 mg/ml and 2 mg/ml dose respectively.

Table-12: Effects of Piperidine Derivatives **(IV-XXXIII)** on Spontaneous Contractions of Isolated Rabbit Jejunum.

S.No.	Compound	Dose (mg/ml)	Response
1	IV	0.3	Relaxant
2	V	0.3	Relaxant
3	VI	0.3	Relaxant
4	VII	1.0	Relaxant
5	VIII	2.0	Inactive
6	IX	2.0	Inactive
7	X	0.1	Relaxant
8	XI	2.0	Relaxant
9	XII	0.3	Relaxant
10	XIII	0.3	Relaxant
11	XIV	0.3	Relaxant
12	XV	0.1	Relaxant
13	XVI	0.5	Relaxant
14	XVII	0.3	Relaxant
15	XVIII	0.7	Relaxant
16	XIX	0.7	Relaxant
17	XX	0.5	Relaxant
18	XXI	0.5	Relaxant
19	XXII	0.1	Relaxant
20	XXIII	0.1	Relaxant
21	XXIV	0.1	Relaxant
22	XXV	0.3	Relaxant
23	XXVI	0.1	Relaxant
24	XXVII	0.1	Relaxant
25	XXVIII	0.1	Relaxant
26	XXIX	0.5	Relaxant
27	XXX	2.0	Inactive
28	XXXI	0.3	Relaxant
29	XXXII	0.3	Relaxant
30	XXXIII	0.3	Relaxant

DISCUSSION

Analgesics fall into one of the several classes of compounds. Perhaps the most important of these is 4-phenylpiperidine group of compounds as it constitutes a morphine fragment. Thus, simplification of the structural requirements for central analgesics activity came from the observation that simple phenylpiperidine "meperidine" shows a biological activity almost indistinguishable from that of morphine (Jacobson, 1970, Lednicer and Mitscher, 1977 and 1980).

A variety of chemical methods are available to increase the analgesic activity of meperidine. One of the methods is the replacement of *N*-CH_3 by selected *N*-substituents such as aralkyl (Beckett *et al.*, 1959, Elpern *et al.*, 1957 and 1958, Orahovat, *et al.*, 1957, Perrine and Eddy, 1956 and Weijlard *et al.*, 1956), propiophenone (Janssen *et al.*, 1958 and 1959a), large alkyl groups (Sterling, 1959), morpholinethyl (Anderson *et al.*, 1956, Green and Ward, 1956, Millar and Stephenson,

1956), alkoxy or phenoxyalkyl (Frearson and Stern, 1958, Morren and Strubbe, 1957).

The preparation of *N*-phenacyl derivatives of alkylated and arylated piperidinols had been reported (Malley and Day, 1957) but not evaluated for possible biological activity. Kugita *et al.*, (1963 and 1965) reported the synthesis and analgesic activity of 3-alkyl-3-phenylpiperidine derivatives. 1-Phenacyl-3-(3-hydroxyphenyl)-3-methylpiperidine (HCl), among this series of compounds, happened to exhibit highest analgesic activity, which was of course equal to that of meperidine and twice that of codeine. Similarly 1-phenacyl-3-(3-hydroxyphenyl)-2,3-dimethylpiperidine (HBr) also showed powerful analgesic activity and it's acute toxicity was greatly lowered.

Most of the compounds under study are substituted phenacyl derivatives of 4-hydroxypiperidine (**I**), 4-hydroxy-4-phenylpiperidine (**II**) and 4-acetyl-4-phenylpiperidine (**III**). Primarily, the idea was to synthesize the compounds closely related to meperidine class of analgesics and subsequently screen for analgesic activity.

Tables 5-8 present the writhing test results of analgesic activity of substituted *N*-phenacyl derivatives of 4-hydroxypiperidine (**IV-XIII**), 4-hydroxy-4-phenylpiperidine (**XIV-XXIII**), 4-acetyl-4-phenylpiperidine (**XXIV-XXXIII**) and adamantyl derivatives (**XXXIV-XXXVII**) along with their parent compounds (**I-III**) in each Table.

4-Hydroxypiperidine (HCl) and 4-hydroxy-4-phenylpiperidine (HCl) did not show analgesic activity upto the dose of 100 mg/kg whereas, 4-acetyl-4-phenylpiperidine (HCl) exhibited 78, 62 and 45% inhibition of acetic acid induced writhing and caused tremor and convulsions during screening at the dose of 12.5, 25 and 50 mg/kg respectively and was lethal at 100 mg/kg dose.

From Tables- 5-7, it can be ensued that maximum protection against acetic acid induced writhing was displayed by the halosubstituted phenacyl derivatives among all the compounds of three series. Rest of the compounds among 4-hydroxypiperidine series were either inactive or slightly active. Similarly the compounds of 4-hydroxy-4-phenylpiperidine series, other than halogen substituted derivatives did not show so promising results.

Although majority of 4-acetyl-4-phenylpiperidine showed good results, yet halogen substituted derivatives were again the most active among all these compounds.

Among the adamantyl derivatives (Table-8), compound **XXXVI** displayed maximum protection against acetic acid induced writhing, whereas three other compounds were slightly active.

All the compounds (**I-XXXVII**) were also evaluated for analgesic activity by tail flick test. None of the compounds was proved to be active by this method, which can be elaborated by the fact that writhing test is simple, sensitive and reproducible for screening weak analgesics, whereas tail flick test is specifically used for screening strong narcotic analgesics (Turner and Hebborn, 1971). It has been well established that not all compounds exhibiting potent antinociceptive activity in acetic acid induced writhing assay are analgesics to be used as potential therapeutic agents (Ong *et al.*, 1979). Other types of drugs besides analgesics which inhibit writhing, are antihistaminics, parasympathomimetics, sympathomimetics, CNS stimulants and adrenergic blocking agents (Turner and Hebborn, 1971).

Since the compounds **XVIII**, **XIX**, **XXII**, **XXIII**, **XXXI**, **XXXII**, **XXXIII** and **XXXVI** displayed maximum percent inhibition of writhing among their respective series of compounds therefore, these eight compounds were selected for studying their effects on brain monoamine levels of male albino mice expecting that further exploration would provide deep insight in assessing their therapeutic activity.

The effects of substituted 1-phenacyl-4-hydroxy-4-phenylpiperidines (**XVIII**, **XIX**, **XXII** and **XXIII**) on mice brain monoamines levels are depicted in Fig. 4-9 whereas Fig. 10-14 present the results of the effects of 4-acetyl-4-phenylpiperidine derivatives (**XXXI**-**XXXIII** and **XXXVI**), on mice brain monoamines level.

From these results, it is evident that pethidine as well as compounds **XIX** and **XXII** among 4-hydroxy-4-phenylpiperidine derivatives and compounds **XXXI**, **XXXIII** and **XXXVI** among the 4-acetyl-4-phenylpiperidine derivatives did not alter 5-HT levels. Only compound **XXIII** increased brain 5-HT levels as compared to control. The levels of 5-HT were decreased significantly by compound **XVIII** as compared to pethidine injected mice. Similarly, **XXXII** was the only compound, among

the series of 4-acetyl-4-phenylpiperidine derivatives which decreased 5-HT levels as compared to control as well as untreated group.

The levels of 5-HIAA were increased by compound **XXII** and **XXIII** among the derivatives of 4-hydroxy-4-phenylpiperidine and compounds **XXXI** and **XXXII** among the 4-acetyl-4-phenyl derivatives. Conversely compounds **XXXIII** and **XXXVI** decreased brain 5-HIAA levels significantly as compared to control and untreated group.

A role of serotonin in the antinociceptive effects of morphine is often described in animal studies (Samanin *et al.*, 1978) and interest continues in the involvement of serotonergic pathways in opiate and non-opiate analgesia (Roberts, 1989 and Sawynok, 1989). However administration of pethidine produced analgesia but did not increase brain serotonin (Kohut and Nicak, 1974). The present study showed that although pethidine administration did not alter brain serotonin metabolism yet increased serotonin functions may have some role in the analgesic effects of **XXII**, **XXIII**, **XXXI** and **XXXIII**. Indeed analgesic potency of these compounds was somewhat greater than that of compounds **XVIII**, **XIX**, **XXXII** and **XXXVI**.

The effects of newly synthesized compounds were also observed on brain catecholamines metabolism in view of possible concern that clinically employed phenylpiperidine analgesics might induce neurotoxic actions on dopamine neurons in the brain (Ross *et al.*, 1986).

DA levels were decreased by only compounds of 4-hydroxy-4-phenylpiperidine series whereas, 4-acetyl-4-phenylpiperidine derivatives did not cause any significant change in brain dopamine levels.

DOPAC concentrations were increased by compound **XXIII** and **XXXVI** one each from respective series. Compounds **XXII** and **XXIII**, among the 4-hydroxy-4-phenylpiperidine series and all the four derivatives of 4-acetyl-4-phenylpiperidine increased brain HVA levels in comparison to control and pethidine treated mice in case of 4-hydroxy-4-phenylpiperidine, and control and untreated group in case of 4-acetyl-4-phenylpiperidine derivatives.

The administration of compounds **XIX**, **XXII**, **XXIII** and pethidine resulted in enhancement of NA levels in brain. Pethidine and compounds **XIX** and **XXIII** manifested almost the

same level of enhancement. Conversely, the administration of compound **XVIII** caused considerable decrease in brain NA levels.

An acute deficiency of DA produced by the synthetic derivatives of 4-hydroxy-4-phenylpiperidine (**XVIII**, **XIX**, **XXII** and **XXIII**) led to the conclusion that these may have neurotoxic effects, particularly on dopaminergic neurons. However an increase in particularly DOPAC concentration by compounds **XXIII** and **XXXVI** and an associated increase in HVA by the same compounds suggested that the observed decrease in DA levels following compound **XXIII** administration may have occurred because of an acute increase in the release of monoamines. In view of reported DA hyperfunction in schizophrenia and serotonin hypofunction in depression, the findings imply that compounds **XVIII**, **XIX** and **XXII** may be of potential use for the treatment of pain associated with schizophrenia, whereas compounds **XXIII** and **XXXVI** may be used as analgesic for depressive individuals.

Since appropriately substituted piperidines often exhibit potent antihypertensive activity (Wellen *et al.*, Van Zweiten *et al.*, Finch, 1975, Archibald 1971 and 1974, Royds *et al.*,

1972), we thought it may be of interest to screen the substituted *N*-phenacyl derivatives of piperidine as well for their effects on mean arterial blood pressure in normotensive anaesthetized rats, with the hope that these structures might afford potential therapeutic agents. The results of these studies are presented in Tables 9-11, along with their parent compounds.

Compound **I** being the starting material of 4-hydroxypiperidine series, exhibited triphasic response at the dose of 30 mg/kg. Only two compounds (**IV**, **XIII**) showed hypotensive response among all the derivatives. Compound **IV** having *para* methyl substituted phenacyl moiety as a part of it's molecule, showed 46.3% fall in blood pressure at 20 mg/kg dose whereas compound **XIII** being *para*-fluoro substituted derivative, displayed hypotensive response at a smaller dose (10 mg/kg) with profound reduction in blood pressure (82.2%). Among the four methoxy derivatives, only *para* methoxy derivative (**VI**) showed hypertensive response (39.8% change in blood pressure) at the dose of 20 mg/kg. Rest of methoxy derivatives as well as compound **IX**, dihydroxy substituted derivative were

altogether devoid of any effect on blood pressure upto the dose of 30 mg/kg.

Compound **X** and **XI**, former being *para* bromo and latter, *para* phenyl substituted derivative exhibited biphasic response (hypotensive followed by hypertensive) at the dose of 10 mg/kg. Like starting material, *para* chloro substituted derivative (**XII**) also showed triphasic response but at a lower dose i.e. 10 mg/kg.

In case of 4-hydroxy-4-phenylpiperidine series (**XIV-XXIII**), appreciable results were obtained. Compound **II**, the precursor of this series, displayed hypertensive response with mild change in blood pressure at the dose of 10 mg/kg but when it's dose was increased to 30 mg/kg, it produced hypotensive response with 28% reduction in blood pressure.

Compounds **XIV**, **XV**, **XVI**, **XVIII**, **XXI** and **XXII** exhibited hypertensive response. Amongst the compounds, *para* bromo substituted derivative (**XXI**) was the most potent, as it caused 89% rise in blood pressure at the dose of 3 mg/kg. Whereas, rest of the derivatives were also active but at 10 mg/kg dose. Compound **XVI** with *para* methoxy substituent at the phenacyl

moiety, was next to the most potent (**XXI**) at the dose of 10mg. *Para* methyl and 2',5'-dimethoxy substituted derivatives (**XIV** and **XVIII**) manifested almost same level of changes in blood pressure at 10 mg/kg dose. Compound **XV** and **XXII** were active at 10 mg/kg dose but caused slight change in blood pressure.

Compound **XVII**, 2',4'-dimethoxy substituted derivative, happened to be the most active among all the hypotensive compounds (**XVII**, **XIX** and **XXIII**) of the series. It exhibited 84% fall in blood pressure at the dose of 3 mg/kg. Rest of two i.e. *para* fluoro and 3',4'-dihydroxy substituted derivatives (**XIX** and **XXIII**) were also highly active as they exhibited hypotensive response with 89 and 88% change in blood pressure respectively at the dose of 10 mg/kg. *Para* phenyl substituted derivative (**XX**) was the only inactive compound upto the dose of 30 mg/kg among all the compounds of this series.

Most of the substituted phenacyl derivatives of 4-acetyl-4-phenylpiperidine (**XXIV-XXXIII**) exhibited promising results in comparison with their parent compound (**III**), which showed hypotensive response with 34% change in blood pressure at 10 mg/kg dose. Amongst this series of compounds, six caused fall

in blood pressure, two were hypertensive and one each was found biphasic and inactive.

Out of hypotensive derivatives, four (**XXIV** and **XXXI-XXXIII**) were active at the dose of 3 mg/kg and two (**XXVII** and **XVIII**) at 10 mg/kg dose. Compound **XXIV** is the *para* methyl substituted phenacyl derivative and caused 62% drop in blood pressure whereas, **XXXI-XXXIII** are all *para* halogenated phenacyl derivatives and lowered the blood pressure of the magnitude of 88, 83 and 39% respectively. *Para* bromo and *para* chloro substituted derivatives (**XXXI** and **XXXII**) manifested almost similar effect on blood pressure while *para* fluoro derivative (**XXXIII**) is lesser active than these. Remaining two hypotensive compounds (**XXVII** and **XXVIII**) were also highly active but at higher dose i.e. 10 mg/kg. Compound **XXVII** and **XXVIII** were both dimethoxy substituted derivatives, caused 79% and 83% change in blood pressure respectively. Only *para* methoxy and 3',4'-dihydroxyphenacyl derivatives (**XXVI** and **XXIX**) displayed hypertensive response with slight change in blood pressure at the dose of 3 and 10 mg/kg respectively.

Meta methoxy phenacyl derivative (**XXV**) was the only one which showed biphasic response (-59, +21) at 10 mg/kg dose. Similarly *para* phenyl substituted derivative (**XXX**) was the sole inactive compound upto the dose of 30 mg/kg among all the compounds of this series.

In the *in vivo* and *in vitro* studies, the compounds **VI**, **XIV-XVI**, **XVIII**, **XXI**, **XXII**, **XXVI** and **XXIX** were found hypertensive as well as spasmolytic (smooth muscle relaxant), while some others (**IV**, **XIII**, **XVII**, **XIX**, **XXIII**, **XXIV**, **XXVII**, **XXVIII** and **XXXI-XXXIII**) were hypotensive along with spasmolytic activity.

It is not unreasonable that norepinephrine (NE) is hypertensive in the anaesthetized rats but exhibits spasmolytic activity in non-vascular smooth muscles (Weiner, 1985). Though the compounds understudy were not tested for the detailed mechanism of action but it can be speculated that this pattern of activity (hypertensive and spasmolytic) may be similar to that of norepinephrine.

However for the compounds which exhibited spasmolytic activity in non-vascular smooth muscle (jejunum) and also lowered blood pressure, different explanation is required. The

calcium channel blocking drugs are well known for their hypotensive action as well as spasmolytic activity, because this class of drugs relaxes both vascular and non-vascular smooth muscles as calcium is involved in all types of smooth muscle contractions (Balton, 1979 and Brading, 1981). Therefore, the hypotensive along with spasmolytic activity observed with some of the test compounds may be explained similar to that of calcium channel blocking activity, though direct evidence is lacking and further studies are needed to confirm this.

CONCLUSION

Drug design constitutes one of the most important aspects of therapeutic discipline. It is infact a complex and interactive process, involving scientists from many disciplines working together to provide many type of informations. In a similar attempt, piperidine nucleus was selected to quaternize with various substituted phenacyl moieties and adamantyl function, resulting compounds were explored for possible biological activity.

These efforts revealed several realities which are as under:

i) *Mono* substituted piperidine derivatives are comparatively less active than 4,4-disubstituted analogues.

ii) Substituted phenacyl as well as adamantyl derivatives of 4-acetyl-4-phenylpiperidine are generally more potent analgesics as compared to 4-hydroxy-4-phenylpiperidine derivatives.

iii) Halogen substitution in the phenacyl part of molecule is more contributing to the biological activity as compared to other substituents present on the phenacyl moiety of compounds understudy.

iv) Evaluation of compounds **XVIII**, **XIX** and **XXII** for analgesic activity as well as their effects on catecholamines and indoleamines suggest that these have exhibited potent analgesic activity and caused acute deficiency of dopamine. Hence these compounds may be of potential use for pain associated with schizophrenia.

v) Compounds **XXIII** and **XXXVI** displayed potent analgesic activity while, former enhanced 5-HT and DOPAC levels more significantly as compared to rest of the test compounds, latter triggered brain DOPAC levels more than any compound of the series. These findings imply that the compounds might be used as analgesics for depressive individuals.

Apart from fruitful efforts for potential analgesics, three compounds (2',4'-dimethoxyphenacyl derivative of 4-hydroxy-4-phenylpiperidine and *bromo* and *chloro* substituted phenacyl derivatives of 4-acetyl-4-phenylpiperidine) were found potent

hypotensive agents and showed relaxant effects on spontaneous contractions of smooth muscle.

It is proposed that further exploration of biological activity in general and detailed mechanism of action of these hypotensive compounds may lead to the synthesis of new therapeutic agents.

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APPENDIX

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1. **M. Saeed**, M. Ashraf and I.H. Choudhry, "Studies on the Stability of 1,4-Benzodiazepine Derivative". *J. Res. (Science) B.Z.U. Multan*, (In Press).

2. Saira Hameed, Z.S. Saify, S.M. Baqar Hadi Naqvi, **M. Saeed**, Abdullah Khan and Mansoor Ahmed, "Design, Synthesis and Pharmacological Evaluation of *N*-Methylpiperidine Derivatives". *J. Isl. Acad. Sci. Turkey*, **5**, 245 (1992).

3. Saira Hameed, Z.S. Saify, Fiaz Ahmed Vaid, **M. Saeed**, Abdullah Khan and Mansoor Ahmad, "Synthesis and Pharmacological Evaluation of *N*-Methylpiperidine Analgesics". *J. Sci. Iran*, (Accepted).

4. Saira Hameed, **M. Saeed**, Abdullah Khan, Mansoor Ahmed, S.S. Nizami and M.H. Kazmi, "Synthesis and Antibacterial Activity of Picoline Derivatives", *J. Isl. Acad. Sci. Turkey*, (Accepted).

5. Z.S. Saify, S. Moazzam Haider, **M. Saeed**, Abdullah Khan, Mansoor Ahmed and B.S. Siddiqui, "Synthesis of Some 7-Azaindole Derivatives. Their Cytotoxicity and Antibacterial Activity". *Pak. J. Sci. Ind. Res.*, (In Press).

6. Z.S. Saify, **M. Saeed**, Abdullah Khan, S. Moazzam Haider, V.U. Ahmad, Atiya Zia and Darakhshan J. Haleem, "Synthesis of Some Piperidine Derivatives of Potential Analgesic Activity". *Proceedings* of 19th IUPAC Symp., University of Karachi, Pakistan, (In Press).

7. Z.S. Saify, **M. Saeed**, S. Moazzam Haider, Anila Yasmeen, Aliya Zafar and Darakhshan J. Haleem, "Studies on the Effects of 4-Hydroxy-4-Phenylpiperidine Derivative (4-HPPD) on Mice Brain Dopamine Metabolism". *Proceedings* of ISBBPS, Univ. Karachi, Pakistan, (In Press).

8. Z.S. Saify, S. Moazzam Haider, **M. Saeed**, Abdullah Khan, Mansoor Ahmed, A.H. Gilani and Anisa Lateef, "Synthesis of Some 7-Azaindole Derivatives Having Potential Therapeutic Activity". *Proceedings* of Ist. Int. Conf. Sci. Chem. Eng., Iran, (In Press).

9. Z.S. Saify, S. Moazzam Haider, **M. Saeed**, Abdullah Khan, Mansoor Ahmed, Anila Yasmeen, Tahira Pervin and Darakhshan J Haleem, "Neurochemical Studies on Some 7-Azaindole Derivatives". *Proceedings* of ISBBPS Univ. Karachi, Pakistan, (In Press).

10. **M. Saeed**, Mansoor, Ahmed, Z.S. Saify, Atiya Zia and V.U. Ahmad, "Synthesis and Analgesic Activity of 4-Acetyl-4-Phenylpiperidine Derivatives", *Drug Res. Germany*, (Submitted).