LEC.2 4 STAGE

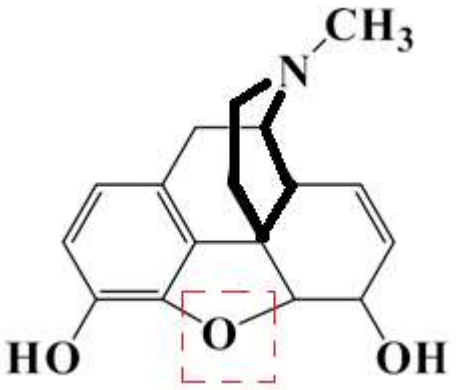
Chemistry II Organic Pharmaceutical

2020-2019

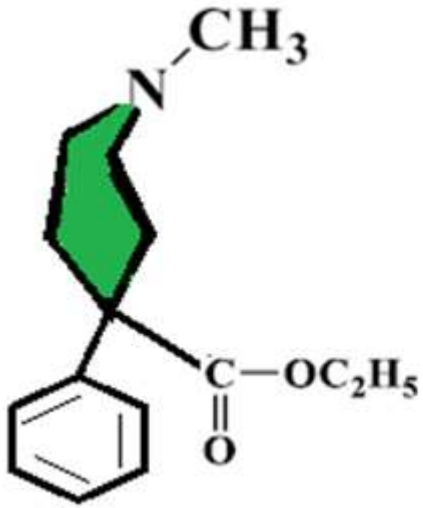
Dr. leaqaa A.

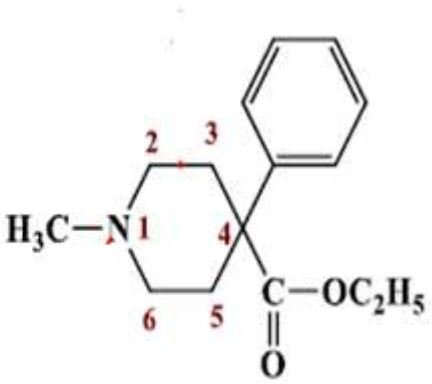
College of Pharmacy, university of Basrah

Modification of ether bridge



Meperidine cpd





activity

- **low potency** at the receptor compared with morphine (0.2%) but

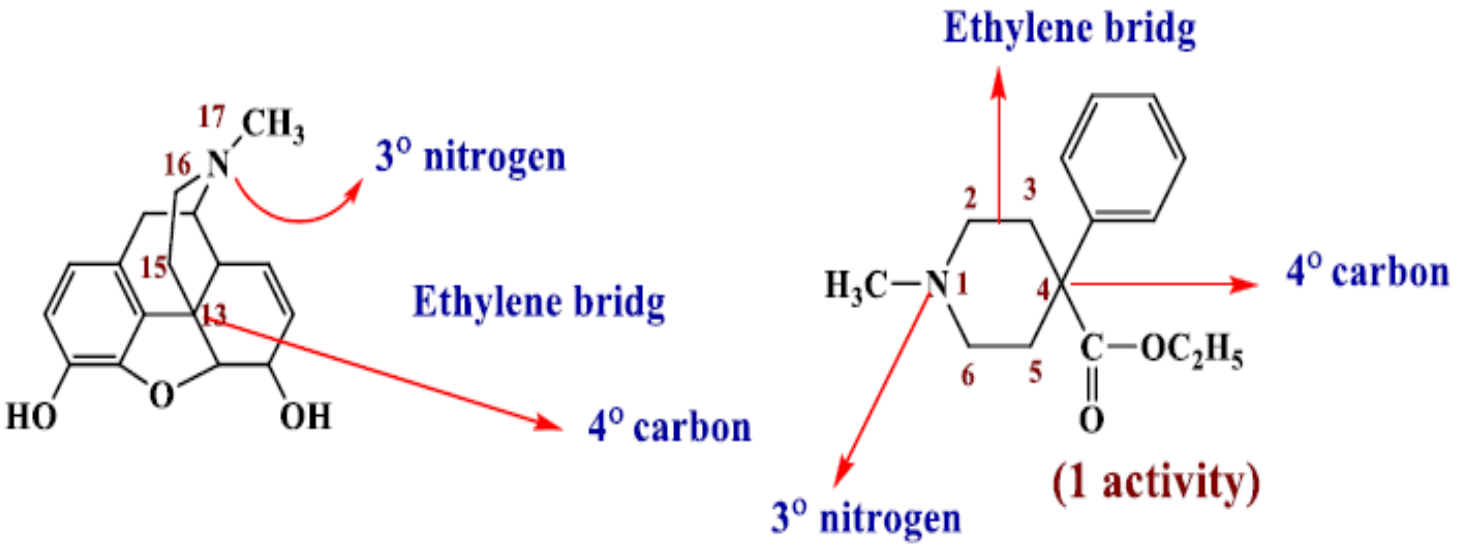
- much higher penetration into the brain

Meperidine quickly penetrates
the BBB and thus has a quick onset of
activity and a high abuse potential.
Meperidine is metabolized
to normeperidin

Meperidine is an agonist at the μ-receptor

SAR for Meperidine analogues

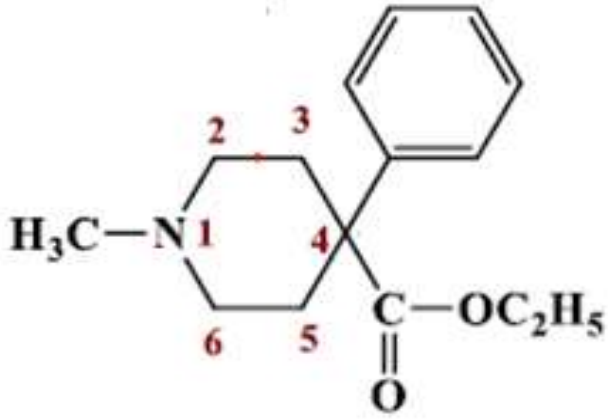
meperidine, possessed analgesic activity, and found to be about one fifth as active as morphine.it was prepared as an antispasmodic.



SAR

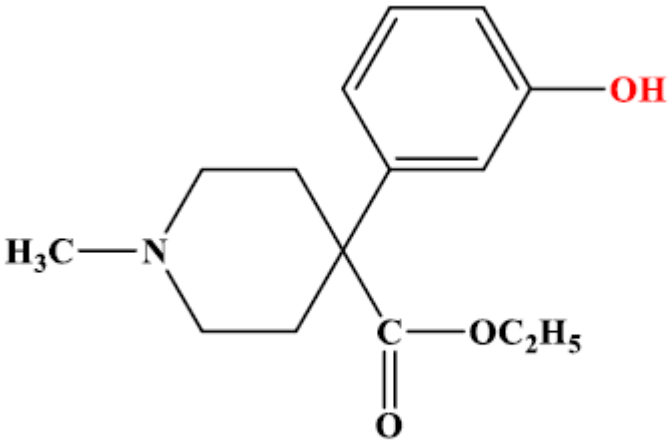
1-Placement of the phenyl and ester groups at the 4 position of 1-methylpiperidine gave optimum activity.

It was found that replacement of the 4-phenyl group by hydrogen , alkyl, aralkyl and heterocyclic groups reduces analgesic activity.



2-The insertion of an *m*-hydroxyl group on the phenyl ring

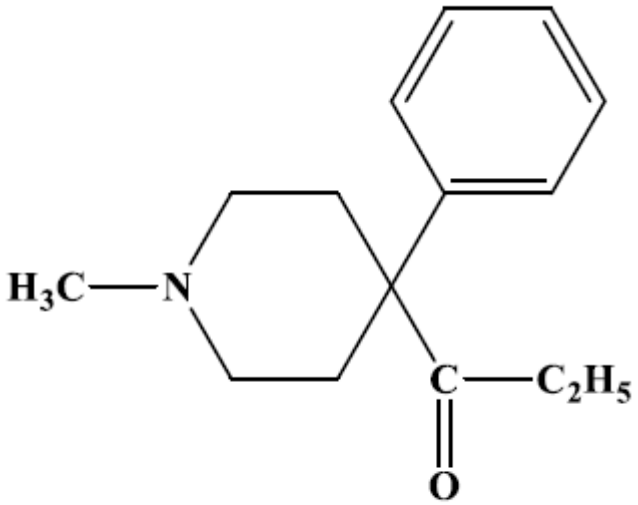
↑analgesic activity.



Bemidone(1.5)

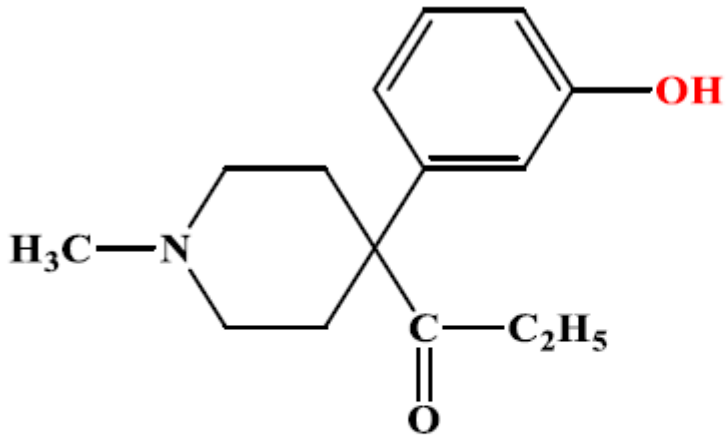
3-Replacement of the 4-ester group by ketone of meperidine,

↓ **analgesic activity.**



(0.5)

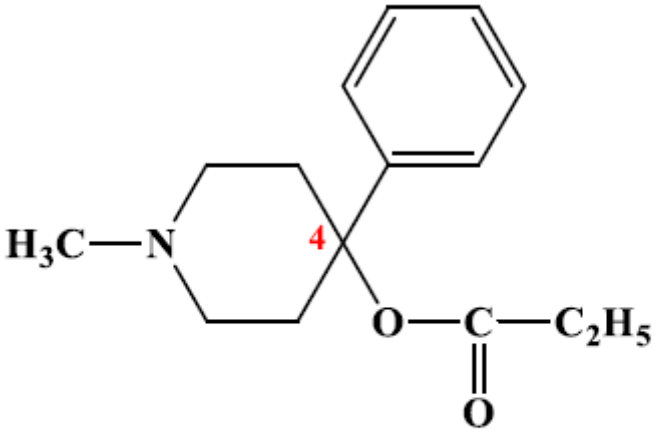
4-Replacement of the 4-ester group by ketone of bemidone, analgesic activity.



Ketobemidone (6.2)

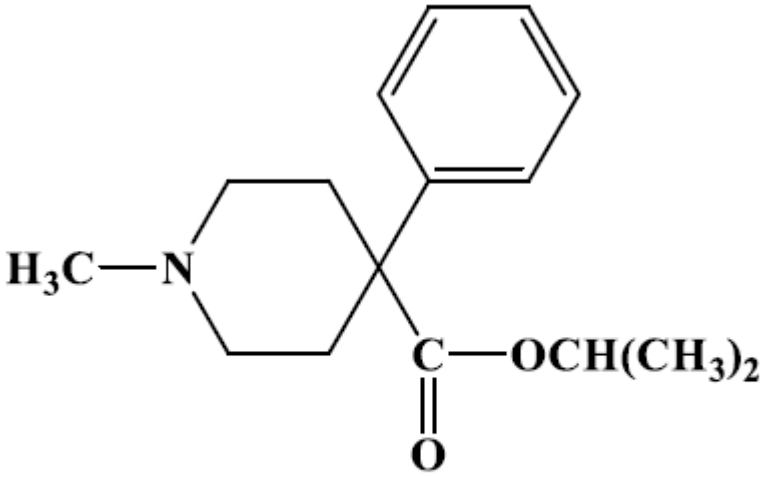
its equivalent to morphine in activity and was once widely used

5- Replacement of the carbethoxyl group in meperidine by acyloxyl groups gave better analgesic, as well as spasmolytic, activity.



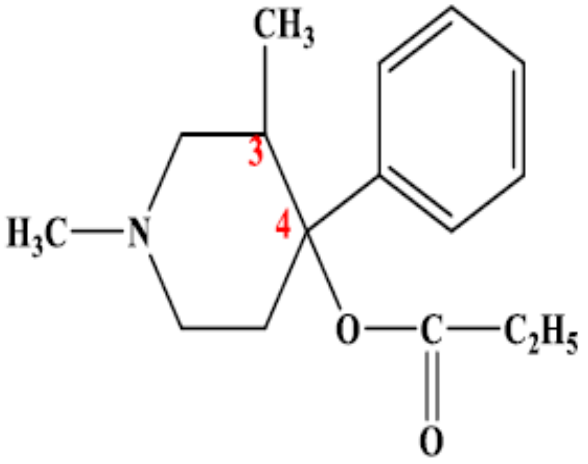
(5) Propionoxy
the reverse ester of meperidine
5 times as active as meperidine

6-Replacement of the carbethoxyl group in meperidine by carboxyisopropyl group results in ↑ in activity.



Properidine (15)

7- introduction of a methyl group into position 3 of the piperidine ring in the propionoxy cpd would yield two isomers, one with activity approximating that of deso morphine and the other with less activity.

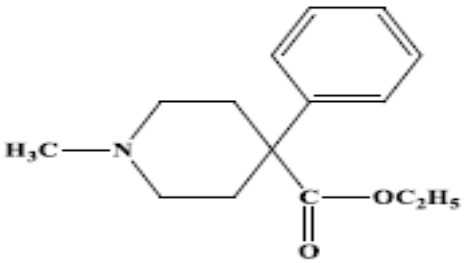


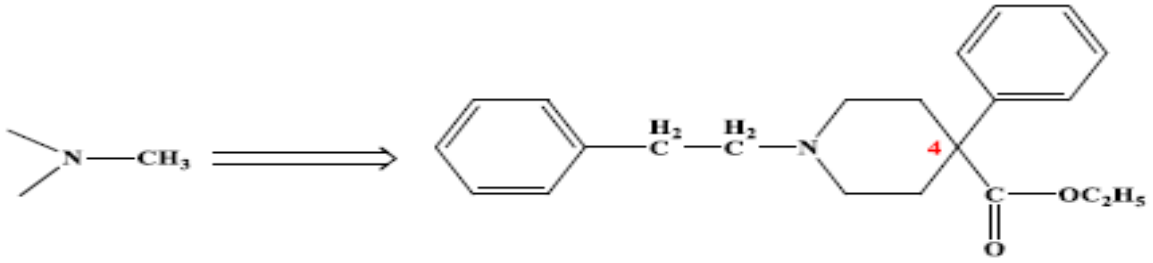
Alphaprodine[trans (methyl/phenyl)] ↓ the activity

Betaprodine[*cis*(methyl/phenyl)] ↑

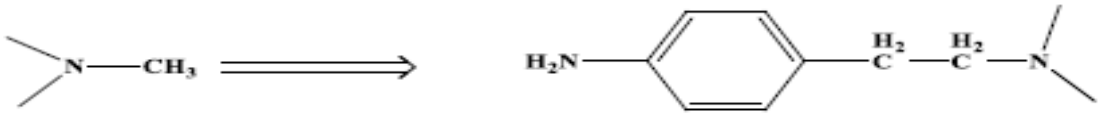
8-Replacement of the N-methyl group by various arylalkyl

groups can ⬆ activity.

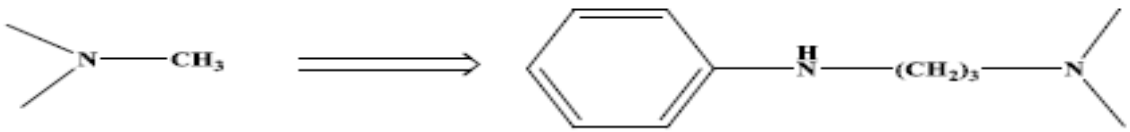




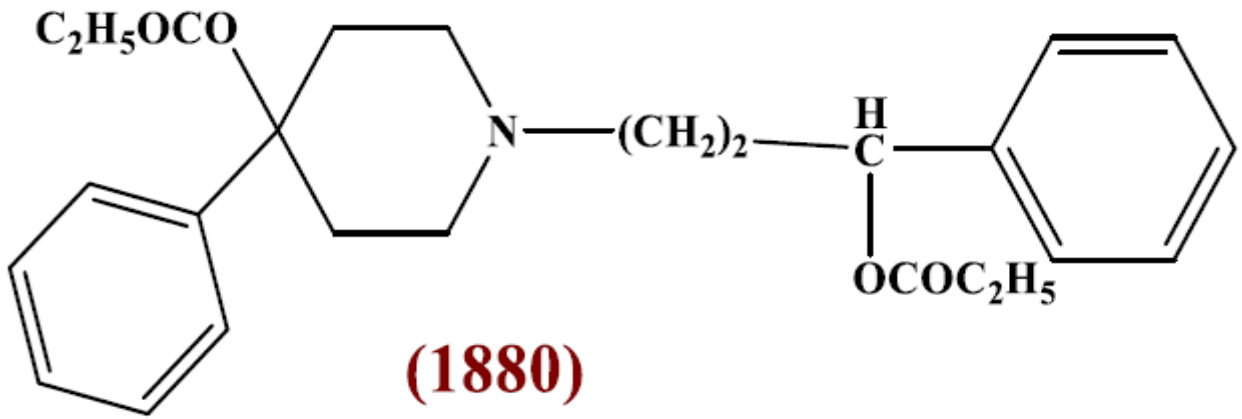
Pheneridine(2.6)
N-Phenylethyl derivative of meperidine
3 times more potent than meperidine



Anilieridine(3.5)

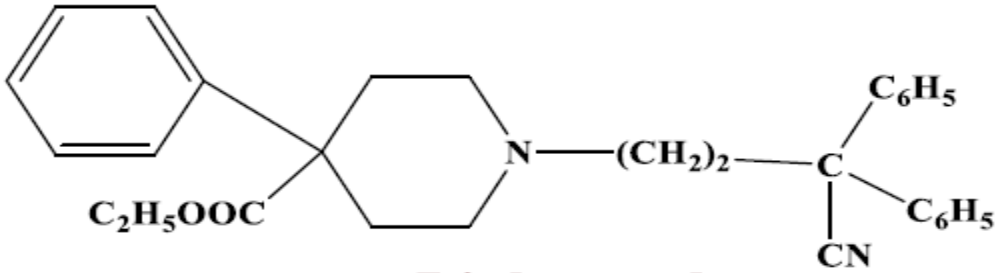


Piminodine(55)
N-Phenylaminopropyl derivative of mepridine



(1880)

N-Phenylpropionoxy derivative of mepridine the most active meperidine type of compound 2000 times as active as meperidine



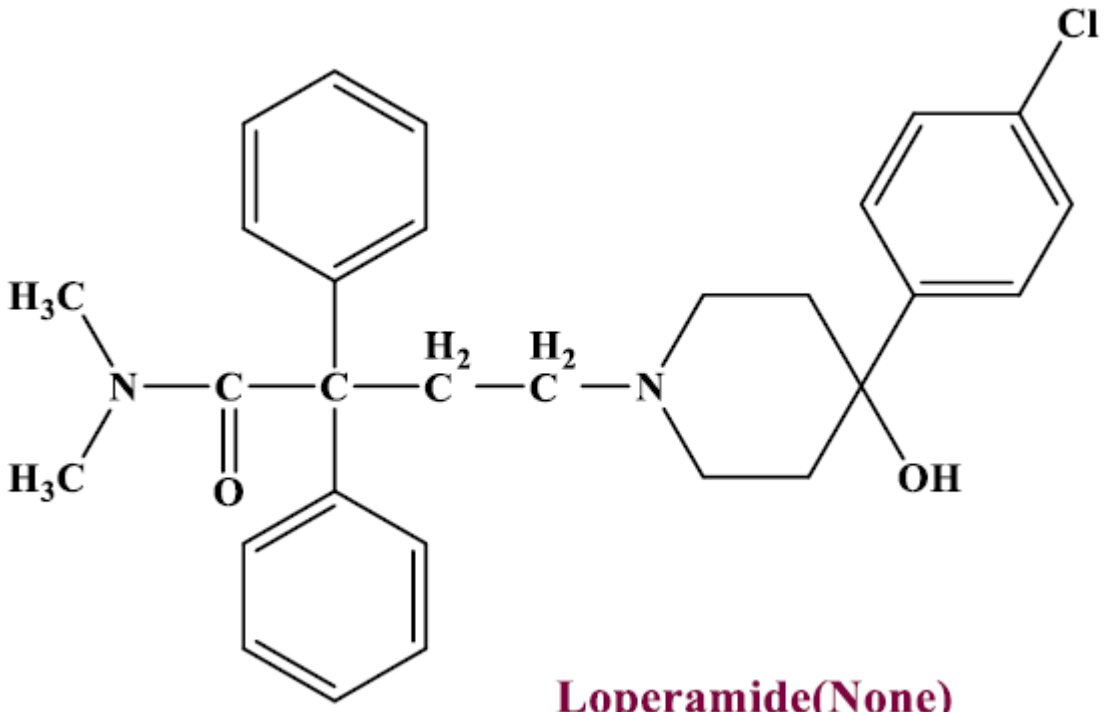
Diphenoxylate

has hybrid structure between meperidine and methadone

have no analgesic activity

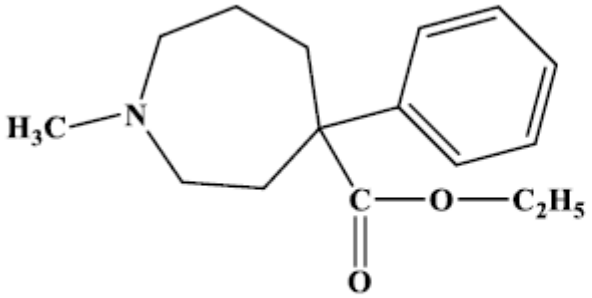
used as intestinal spasmolytic and used for the treatment of diarrhea

Replacement of the 4-phenyl group by *P*-chlorophenyl group, ester group at position 4 by (OH), and N-methyl group by $-CH_2CH_2C(C_6H5)_2C=ON(CH_3)_2$ to give loperamide, which is bind to the opiate receptor in the brain but does not penetrate BBB enough to produce analgesic(have no analgesic activity) so used only as antispasmodic.

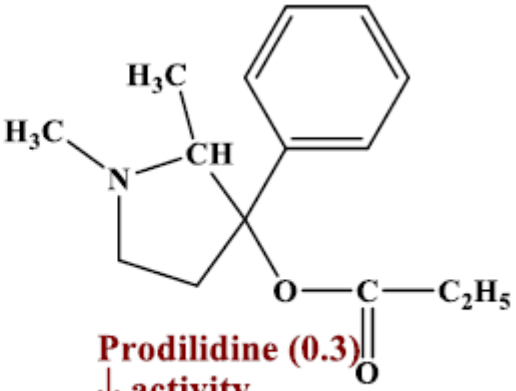


Loperamide(None)

* Enlargement of the ring to 7-member ring (i,e: R= -CH_2-CH_2-CH_2), or reduce its size to 5-member ring (i,e: R= -CH2-) lead to decrease the activity.

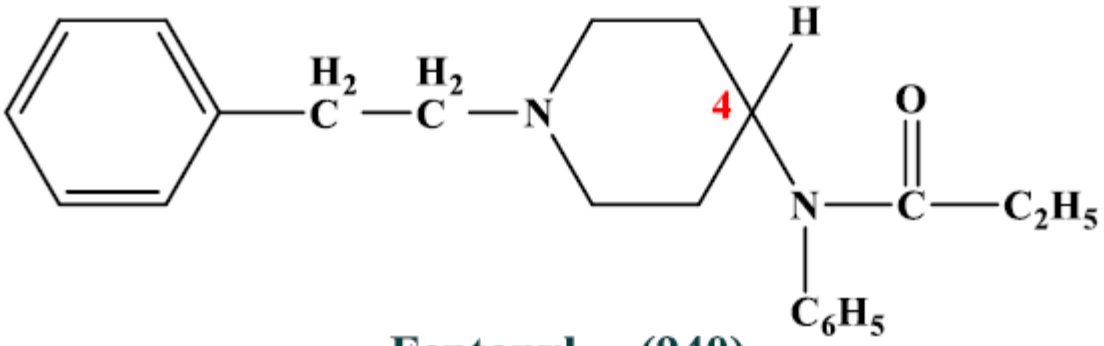


Ethoheptazine(1)
↓ activity

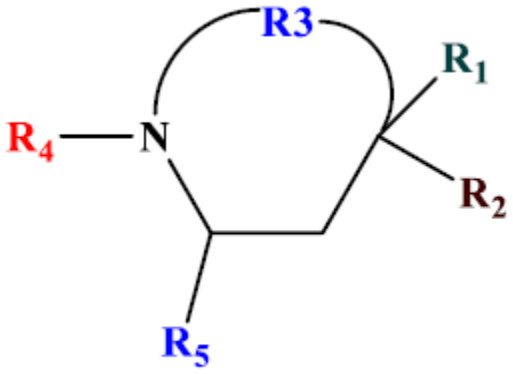


Prodilidine (0.3)
↓ activity

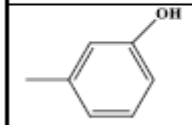
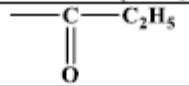
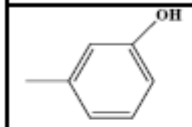
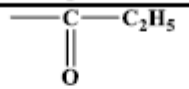
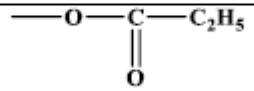
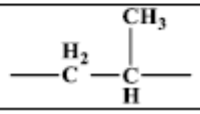
fentanyl in which the phenyl and the acyl groups are separated from the ring by a nitrogen. It is a powerful analgesic, 50 times stronger than morphine in humans, with minimal side effects.

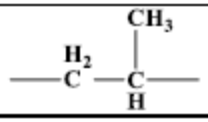
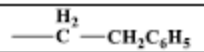
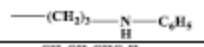
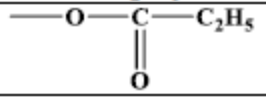
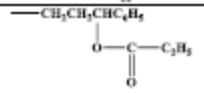
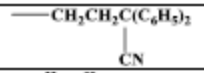
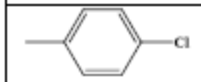
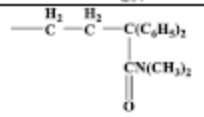
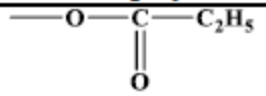
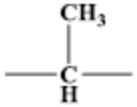
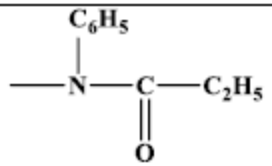
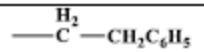


Fentanyl (940)



Meperidine

R1	R2	R3	R4	Name	Activity relation to meperidine
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$	$-CH_3$	Meperidine	1
	$-COOC_2H_5$	$-CH_2-CH_2-$	$-CH_3$	Bemidone	1.5 ↑
$-C_6H_5$	$-COOCH(CH_3)_2$	$-CH_2-CH_2-$	$-CH_3$	Properidine	15↑
$-C_6H_5$		$-CH_2-CH_2-$	$-CH_3$		0.5↓
		$-CH_2-CH_2-$	$-CH_3$	Ketobemidone	6.5↑
$-C_6H_5$		$-CH_2-CH_2-$	$-CH_3$		5↑
$-C_6H_5$			$-CH_3$	Alphaprodine Betaprodine	5↑ 14↑

$-C_6H_5$			$-CH_3$ (R5=CH_3)	Trimepridine	7.5↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Pheneridine	2.6↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Anileridine	3.5↑
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Piminodine	55↑
$-C_6H_5$		$-CH_2-CH_2-$			1880
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-$		Diphenoxylate	None
	-OH	$-CH_2-CH_2-$		Loperamide	None
$-C_6H_5$	$-COOC_2H_5$	$-CH_2-CH_2-CH_2-$	$-CH_3$	Ethoheptazine	1
$-C_6H_5$			$-CH_3$	Prodilidine	0.3
H		$-CH_2-CH_2-$		Fentanyl	940