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CHAPTER 5
STRUCTURE ACTIVITY RELATIONSHIPS OF PHENCYCLIDINE DERIVATIVES

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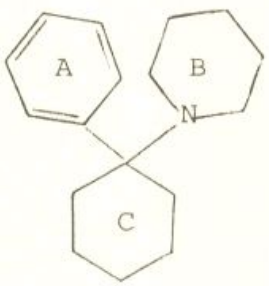
The discovery of the pharmacological properties of 1-(1-phencyclohexyl)piperidine (phencyclidine, PCP) and its proliferation as an illicit hallucinogenic agent has induced a wave of research directed toward understanding its mode of action, development of countermeasures against poisoning, identification, detection, etc.

Many reviews on PCP (Balster and Pross, 1978; Domino, 1964, 1978a; Petersen and Stillman, 1978) have dealt primarily with the pharmacological, biochemical and medical aspects of PCP intoxication. The present review summarizes the activities of various substituted 1-aryl (alkyl) cycloalkylamines related to PCP.

The structural modifications can be classified as a) replacement of each of the three rings A, B and C of the PCP molecule by a different group, and b) introduction of substituents into these rings.



Phencyclidine (PCP)

The activity of PCP congeners was estimated by an array of methods that included: anticholinesterase activity and interaction with the muscarinic receptor (Kalir et al., 1978; Kloog et al., 1977; Maayani et al., 1974; Vincent et al., 1978), mydriatic activity (Maayani et al., 1974), interaction with the opiate receptor (Vincent et al., 1978), cataleptic activity and antitonic extensor properties

(Maddox et al., 1964), rotarod performance (Geneste et al., 1979; Kalir et al., 1969, 1975; Mousseron et al., 1966, 1968; Vincent et al., 1979; Zukin and Zukin, 1979), spontaneous EEG (Gehrmann and Killam, 1979), and a variety of behavioral tests (Brady et al., 1979; Kalir et al., 1969, 1975; Shannon, 1979). Notwithstanding the fact that the studies were carried out in different preparations and animals, the results were usually compatible.

A.1. Replacement of the phenyl group (Table 1)*

Exchange of phenyl by a thienyl group enhanced central activity (Brady et al., 1979; Gehrmann and Killam, 1979; Geneste et al., 1979; Kalir et al., 1969, 1975; Shannon, 1979; Vincent et al., 1979). The bulky 1-naphthyl and 9-fluorenyl derivatives were inactive (Maddox et al., 1964). Introduction of an aliphatic substituent instead of phenyl brought about a sharp drop in central effects (Kalir et al., 1980; Lotan and Kalir, 1975; Mousseron et al., 1966). In the aliphatic series compounds bearing a three carbon chain were the most active. The potency was enhanced by introducing an unsaturated bond. The propargyl derivative, when tested in monkeys, produced PCP-like effects, thus suggesting a hallucinogenic property.

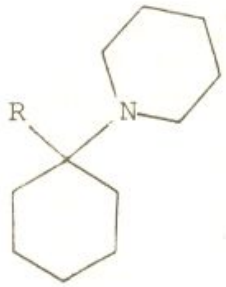
The order of central potency of these compounds does not correlate with inhibition of butyrylcholinesterase (Lotan and Kalir, 1975; Maayani et al., 1974).

A.2. Substitution at the aromatic ring (Table 2)

The effect of the aromatic substitution has been studied with respect to the nature and position of the substituents (Geneste et al., 1979; Kalir et al., 1969, 1978; Maddox et al., 1964; Maayani et al., 1974; Teomy et al., 1979). Central activity was enhanced by nucleophilic substitution, particularly by the free amino and hydroxy groups. Compounds bearing electrophilic substituents like F, Cl and NO_2 did not reveal any appreciable effect. Derivatives substituted at meta position were stronger than their para isomers. In this series there was an increase of the effect on butyrylcholinesterase along with the increase of the electron density in the phenyl ring. The affinity for the muscarinic receptor did not follow the same trend

*In this and subsequent tables, only relative values of potency (PCP=100) are given. The compounds are listed in order of descending central activity.

Table 1. Relative potency of 1-substituted PCP analogs

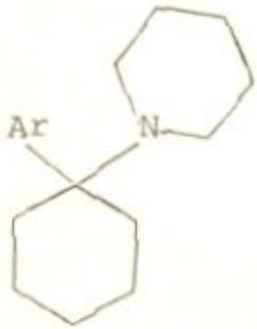


R	Central potency	Inhibition of butyrylcholinesterase
2-Thienyl	300	
3-Thienyl	100-150	
Ph (PCP)	100[a]	100[b]
CH_2=$CHCH_2$-	25-100	190
CH_2=CH-	5	200
$CH_3(CH_2)_2$-	5	8
CH≡CCH_2-	4-5	6
CH_3CH_2-	2-3	34
$CH_3(CH_2)_3$-	2	
$CH_3(CH_2)_7$-	0	
1-Naphthyl	0	
9-Fluorenyl	0	
CH≡C-		28-43
$PhCH_2$-		23
CH_3C≡C-		5

[a] ED_{50}=8 mg/kg (rotarod, mice) (Mousseron et al., 1966, 1978; Geneste et al., 1979).

[b] $K_i=5.1 \times 10^{-7}$ (Kloog et al., 1977).

Table 2. Relative potency of phenyl substituted PCP derivatives



Ar	Central potency	Inhibition of butyrylcholinesterase
$3\text{-}H_2NC_6H_4\text{-}$	300-800	
$3\text{-}HOC_6H_4\text{-}$	200	
$3\text{-}MeOC_6H_4\text{-}$	170	
$C_6H_5\text{-}$ (PCP)	100	100
$4\text{-}MeOC_6H_4\text{-}$	40	200-400
$2\text{-}MeOC_6H_4\text{-}$	30	
$4\text{-}MeO\text{-}3\text{-}MeC_6H_3\text{-}$		650
$3,4\text{-}OCMe_2OC_6H_3\text{-}$		420
$3,4\text{-}(MeO)_2C_6H_3\text{-}$	7	350
$4\text{-}MeSC_6H_4\text{-}$		250
$4\text{-}ClC_6H_4\text{-}$	0	130
$4\text{-}FC_6H_4\text{-}$	0	80
$3\text{-}O_2NC_6H_4\text{-}$	0	
$4\text{-}O_2NC_6H_4\text{-}$	0	

(Kloog et al., 1977; Teomy et al., 1979). The mydriatic activity (much weaker than that of atropine) was most pronounced for phenyl, thienyl and 4-tolyl compounds, moderate for alkyl and benzyl derivatives, and absent for 4-halo and 4-methoxy congeners (Kloog et al., 1977).

B.1. Replacement of the piperidine ring (Table 3)

A substantial number of PCP analogs with a different heterocyclic ring or an alkylamino group instead of piperidine have been prepared (Kalir et al., 1969, 1975, 1980; Maddox et al., 1964; Mousseron et al., 1966, 1968). The most potent compound is the N-ethyl analog. The pyrrolidine derivative is also more active than PCP. The N-allyl compounds were prepared as potential PCP antagonists. They did not exhibit any such property, but were active in some behavioral tests. The behavioral changes elicited in rats by the diallyl derivative resembled those produced by DMT and LSD (Kalir et al., 1980).

The antibutyrylcholinesterase potency depended on the structural changes in the region of the cationic head, and was low for primary and secondary amines, higher for the tertiary derivatives, and highest for the quaternary PCP methiodide (Kloog et al., 1977). A similar trend was observed for the muscarinic receptor affinity (Kalir et al., 1980; Kloog et al., 1977).

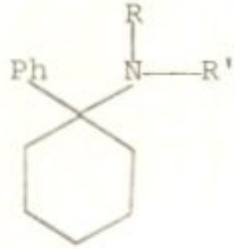
B.2. Piperidine substituted PCP derivatives (Fig. 1)

Only a few PCP analogs substituted at the heterocyclic ring have been reported. The 3-methyl derivative revealed some activity while the 4-substituted methyl and dimethyl compounds were inactive (Maddox et al., 1964; Kalir et al., 1969). The 4-hydroxy derivative - a known metabolite of PCP (Wong and Bieman, 1975) - was approximately ten times less active than the parent compound (Domino, 1978b). Its esters were tested as analgesics (Itshak et al., 1980).

C.1. Replacement of the cyclohexane ring (Table 4)

PCP analogs with a different cycloalkyl heterocycloalkyl or a tricyclic substituent were less potent than the parent compound. The effect of exchanging a CH_2 link in cyclohexane by sulfur - but not by nitrogen - was less pronounced than of altering the ring size (Geneste et al., 1979; Kalir et al., 1969, 1975; Mousseron et al., 1968). The derivative of adamantane had antiacetylcholine potency

Table 3. Relative potency of N-substituted 1-phenylcyclohexylamines



R	R'	Central activity[a]	Inhibition of butyrylcholinesterase	Affinity for the muscarinic receptor
H	Et	200-250	2	12
	$-(CH_2)_4-$	120		
	$-(CH_2)_5-$ (PCP)	100	100	100[b]
$-CH_2CH_2CH=CH_2CH_2-$				
H	Me			
H	n-Pr			
H	$CH_2=CHCH_2-$		2	13
$CH_2=CHCH_2-$	$CH_2=CHCH_2-$		100	36

Et	$CH_2=CHCH_2-$		20	65
Me	$CH_2=CHCH_2-$		2	59
H	iso-Pr			
Me	Et			
Me	Me			
H	$MeO(CH_2)_2-$			
H	H		2	3
$-CH_2CH_2OCH_2CH_2-$		12		
Et	Et			
-CH=CHCH=CH-		0		
PCP.MeI		0	220	270

[a]Many compounds were reported as centrally active without further details.

[b]$K_d = 9.1 \times 10^{-6}$ (Kloog et al., 1977).

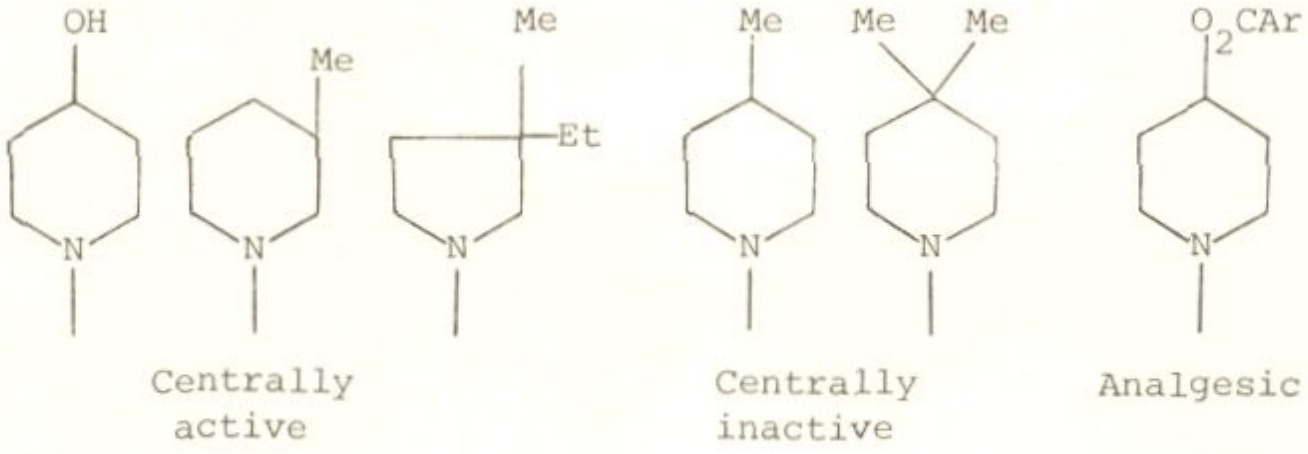
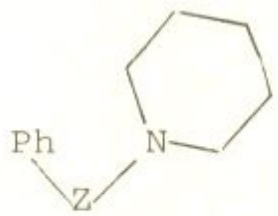


Fig. 1. Activity of piperidine substituted PCP derivatives (only the ring B is shown).

Note that the type and position of the piperidine substituted group markedly alters pharmacological activity. Some derivatives show various degrees of central activity, while others are relatively inactive. Introduction of a phenyl substituent into the 4-position produces compounds with narcotic analgesic activity.

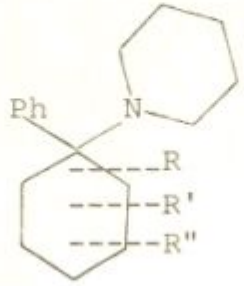
Table 4. Relative potency of cycloalkyl and bicycloalkyl PCP analogs



Z (ring)	Central potency	Affinity for the muscarinic receptor
Cyclohexane (PCP)	100	100
4-Thiacyclohexane	45	
Cyclopentane	25	
Cyclobutane	20	
N-Methyl-4-piperidine	14	
3-Quinuclidine	0	
2-Adamantane	0	800-1000[a]

[a]The value for 2-phenyl-2-adamantamine was 30.

Table 5. Relative potency of cyclohexane substituted PCP analogs



Substituent, position conformation[a]						Central activity	Affinity for receptor		
							Muscarinic	Opiate	PCP
Ph	R		R'	R"					
(a)	4Me	(e)	H	H		145	9000	260	190
(a)	2Me	(a)	H	H		110	700	235	210
	H		H	H	(PCP)	100	100	100[b]	100[c]
(a)	2MeO	(a)	H	H		40			30
(a)	3Me	(e)	H	H		35	680	215	42
	4Me		4Me	H		8			5

(e)	3Me	3Me	5Me(e)	8			
(a)	4-tBu(e)	H	H	5	300	65	1
(e)	4-tBu(e)	H	H	5	4	0	0
	4-OH	H	H	3			
(e)	2Me (a)	H	H	0	1300	160	3
(e)	4Me (e)	H	H	0	370	260	0
(e)	2Me0 (a)	H	H	0			0

[a](a)-axial; (e)-equatorial

[b]$K_{0.5}$=26 µM (Vincent et al., 1978).

[c]IC_{50}=0.23-0.25 µM (Vincent et al., 1979; Zukin and Zukin, 1979).

equal to that of PCP and a much higher affinity for the muscarinic receptor (Kloog et al., 1970; Gabrialewitz et al., 1980).

C.2. Cyclohexane substituted PCP derivatives (Table 5)

The potency of cyclohexane substituted PCPs was studied with regard to the nature of substituents, their position and conformation. Introduction of a methyl group reduced the central activity (Kalir et al., 1975). Nevertheless, some of the conformational isomers were more active than PCP itself and it has been stated that the more potent conformers have the ability to adopt an axial aryl and equatorial piperidine conformation (Geneste et al., 1979). Methoxy derivatives were less active and introduction of several methyls or a bulky tert-butyl group abolished the activity. The 4-hydroxy derivative, which was detected as a PCP metabolite (Wong and Bieman, 1975), was found to be 30 times weaker than PCP (Domino, 1978b). Thienyl analogs were more active than the corresponding phenyl compounds. There was no apparent correlation between central potency and affinity to the muscarinic or opiate receptor (Vincent et al., 1978). A correlation between central activity and affinity to an alleged PCP receptor was reported recently (Vincent et al., 1979; Zukin and Zukin, 1979).

Summary

Modification of the structure of PCP involves either replacement of the phenyl, cyclohexyl, and piperidine rings or the introduction of substituents onto those rings. The activity of the congeners of PCP were studied by a variety of techniques.

Replacement of the phenyl ring with a thienyl ring enhanced central activity but bulkier aromatic rings were inactive. Aliphatic replacements also had a large reduction in activity. The addition of nucleophilic substituents (e.g., NH_2, OH) enhanced activity whereas electrophilic substitutions (e.g., F, Cl, NO_2) were essentially inactive.

PCP analogs with changes in the heterocyclic ring were also studied. Pyrrolidine and tetrahydropyridine analogs were similar to PCP in their activity while the morpholine congener was less active and pyrrole was inactive. Those compounds with a substituent on the piperidine ring were less potent than PCP; the 4-hydroxy derivative (a known metabolite of PCP) had 10% of the potency of PCP.

Those compounds with changes in the cyclohexyl ring were

also less potent than the parent compound. PCP analogs with cycloalkyl rings of different size showed a reduced activity, although the adamantane derivative had a much greater affinity for the muscarinic receptor than PCP. The introduction of a methyl group on the cyclohexyl ring reduced central activity (with the possible exception of the 4-methyl compound) and those compounds with two methyls, tert-butyl and benzyloxy substituents were inactive.

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