was washed with H_2O and evaporated to near dryness. The oily residue was allowed to stand in a moist atmosphere until it solidified (ca. 1 h): yield 1.7 g. Purification was effected by twice dissolving in Et_2O (carbon) and concentrating.

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[1-[3-(Phenothiazin-10-yl)propyl]-4-piperidinyl]phenylmethanones, a Novel Class of Long-Acting Neuroleptic Agents

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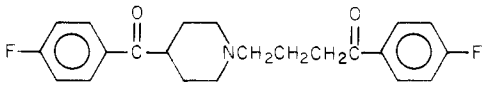
In previous studies the phenyl-4-piperidinylmethanone moiety was shown to be a neuroleptic pharmacophore. A short series of [1-[3-(phenothiazin-10-yl)propyl]-4-piperidinyl]phenylmethanones was prepared and tested for neuroleptic activity using the blockade of *d*-amphetamine lethality in aggregated mice and suppression of conditioned avoidance behavior as the end points. Most compounds were shown to be potent neuroleptic agents and two were found to possess a long duration of action.

An earlier report from this laboratory[1] described the preparation and neuroleptic activity of a series of *N*-alkyl-4-benzoylpiperidines. The structure–activity data suggested that the benzoylpiperidine moiety is a potent neuroleptic pharmacophore comparable to a butyrophenone group. One of the compounds in the series, **1**,[2] which combines both pharmacophores into a single molecule has proven to be a highly effective neuroleptic agent in clinical trials in man. These results prompted us to prepare and test a short series of phenothiazine derivatives (**2–6**) which coupled the benzoylpiperidine pharmacophore with the 10-phenothiazinylpropyl group.



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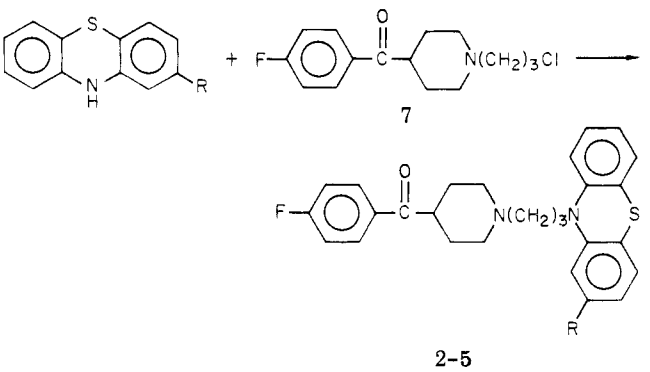
Chemistry. Compounds **2–5** (Table I) were prepared by reacting 1-(3-chloropropyl)-4-(4-fluorobenzoyl)piperidine (**7**) with the appropriately substituted phenothiazine (Scheme I). Compound **6** was prepared by reacting 2-chloro-10-(3-chloropropyl)phenothiazine (**8**) with 4-(3,4-dichlorobenzoyl)piperidine (**9**) (Scheme II). Column chromatography on Florisil, short-path distillation, or salt formation was used to purify compounds **2–6**. The intermediates **7** and **9** were prepared according to Schemes III and IV, respectively. The synthesis of **2** given in the Experimental Section is representative of the synthesis of compounds **2–6**. Compound **8** was prepared by a modification of a published synthesis of 3-chloro-10-(3-chloropropyl)phenothiazine.[3]

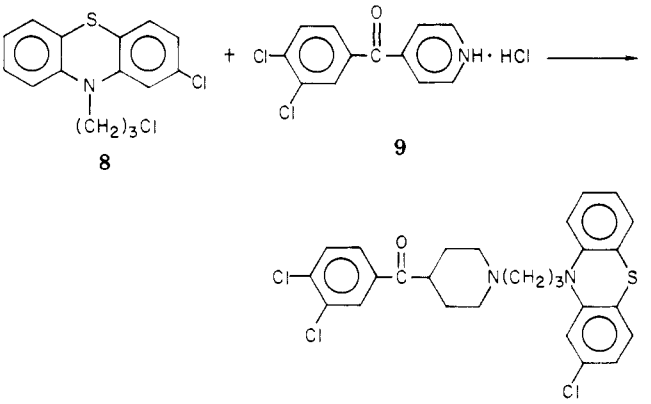
Compounds were tested for neuroleptic activity using blockade of *d*-amphetamine lethality in aggregated mice and suppression of conditioned avoidance behavior in trained mice as the end points. For the former method, groups of ten, adult, female mice (ICR–DUB strain) were given geometrically spaced doses of test compound at predetermined intervals (1 h to 7 days) prior to a dose of *d*-amphetamine (21 mg/kg ip) that was known to be lethal to 90% of the animals. Each group of animals was placed in a separate wire mesh cage (60 in.^{2} of floor space), and after 24 h the number of surviving animals was determined.

Scheme I



7 **2–5**

Scheme II



8 **9** **6**

ED_{50} values were determined[4] and defined as the dose that prevented death in 50% of the mice.

Compounds **2** and **3** were as potent as the reference standards, haloperidol and chlorpromazine, when a 1-h pretreatment time was used (Table II). With longer pretreatment times, compound **2** retained its potency whereas the reference agents soon became ineffective. For example, with a 3-day pretreatment time, even doses of the reference agents approaching their LD_{50} values were

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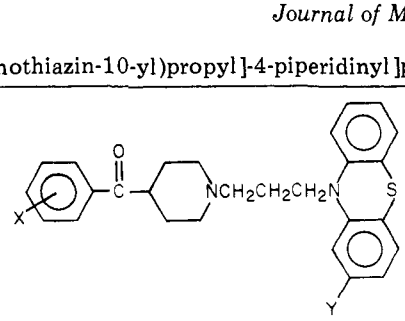
Table I. Physical Properties of [1-[3-(Phenothiazin-10-yl)propyl]-4-piperidinyl]phenylmethanones



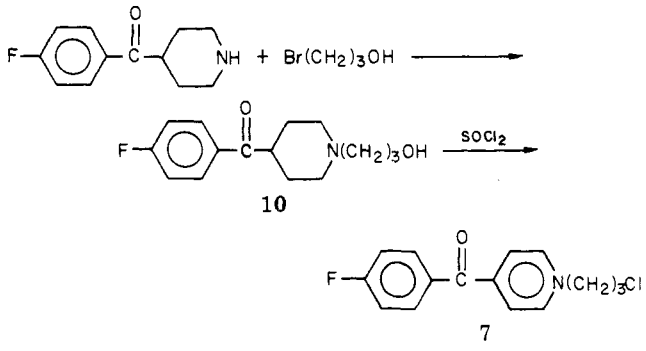
No.	X	Y	Yield, %	Mp, °C	Formula[a]	Recrystn solvent[b]
2	4-F	Cl	20	188-189	$C_{31}H_{30}N_2O_5FClS$[c]	M
3	4-F	$COCH_3$	24.5	146-149	$C_{74}H_{80}N_4O_{23}S_2F_2$[d]	A-PE
4	4-F	H	40.5	190-192	$C_{124}H_{126}N_8O_{21}S_4F_4$[e]	M-IE
5	4-F	CF_3	61.6	158.5-161	$C_{32}H_{30}N_2O_5SF_4$[c]	IA-IE
6	3,4-Cl_2	Cl	58	143.5-145.5	$C_{27}H_{25}Cl_3N_2OS$[f]	B-O

[a] All compounds were analyzed for C, H, and N. [b] A = acetone, B = benzene, IA = isopropyl alcohol, IE = isopropyl ether, M = methanol, O = isooctane, PE = petroleum ether (30-60 °C). [c] Fumarate salt. [d] Difumarate·1.5hydrate, $(C_{29}H_{29}FN_2O_2S)_2(C_4H_4O_4)_4\cdot 3H_2O$. [e] Fumarate·0.25hydrate, $(C_{27}H_{27}FN_2OS)_4(C_4H_4O_4)_4\cdot H_2O$. [f] Free base.

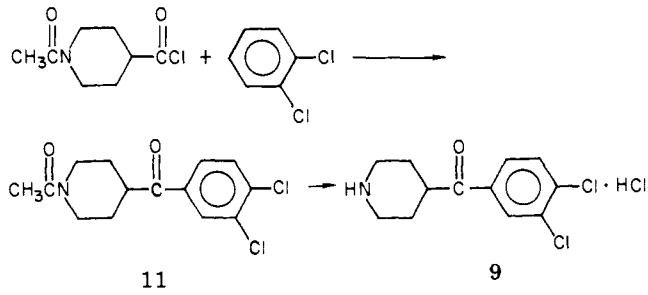
Table II. Blockade of *d*-Amphetamine Lethality in Aggregated Mice

Compd	Protective ED_{50}, mg/kg ip								
	1 h	4 h	16 h	2 days	3 days	4 days	5 days	6 days	7 days
2	0.17	0.53	0.72	4.6	8.8	20.9	>60.0		
3	0.14	0.10	0.76	22.5	17.5	>64.0	60.0		
4	0.94	0.35	1.27	12.1	>50.0				
5	1.44	3.50	1.89	4.7	15.2	27.0	28.4	26.5	45.5
6	>16								
Haloperidol	0.09		0.58	16.0	$>LD_{50}$				
Chlorpromazine	0.28		3.65	>32.0	$>LD_{50}$				
Penfluridol	1.28	1.82	1.52	3.0	17.0	47.5	$>LD_{50}$		

Scheme III



Scheme IV



ineffective in protecting from *d*-amphetamine lethality. Although compound **3** was active in low doses during the first day, markedly higher doses were necessary when the pretreatment period was extended to 2 days and beyond. Of interest was compound **5**, which was significantly less potent than compounds **2** or **3** when the pretreatment time was less than 1 day. With longer intervals between test compound and *d*-amphetamine administration, compound **5** was equal to or superior to compound **2**, as well as to penfluridol, a clinically effective long-acting neuroleptic. In fact, after 7 days, an ED_{50} was calculated for compound **5**, whereas all other compounds tested were inactive. Compound **5** (50 mg/kg ip) produced marked CNS depression of approximately 24-h duration, followed by mild sedation during the remaining 6 days. The animals did not lose weight during this study and they groomed normally (except for the first 24 h). In contrast, animals given a large dose (60 mg/kg ip) of compound **2** were very depressed during the 5-day pretreatment period. They ate very little and failed to groom their coats.

Conditioned avoidance behavior was tested using a modification of the method of McKean and Pearl.[5] Adult, female mice were trained to jump from a grid to an elevated platform to avoid an electrical shock to their feet. An electrically activated solenoid pushed the mouse back onto the grid 20 s later and the animal had 5 s to avoid the next shock by returning to the platform. Upon reaching criterion of 90–100% correct avoidance responses, groups of mice (N = 3–5 per dose) received 10 mg/kg ip of test drug or reference agent. Twenty trials were run prior to and at periodic intervals after drug administration. Percent correct avoidance responses were determined at each time interval for each animal and means were determined.

As indicated in Table III, compound **5** had a duration of action in suppressing conditioned avoidance responding greater than 3 days. None of the other test compounds was active at 2 days and chlorpromazine was essentially inactive after 1 day. In another separate study not reported here, 20 mg/kg ip of penfluridol produced marked suppression of conditioned avoidance behavior in mice with a duration of action of approximately 7 days.

Compounds that block *d*-amphetamine lethality in low doses and suppress conditioned avoidance behavior in larger doses are classified as potential major tranquilizers.[6] Because of the combination of two neuroleptic pharmacophores, it was not surprising that this was the primary

Table III. Suppression of Conditioned Avoidance Behavior in Mice by 10 mg/kg ip of Test Compound or Reference Agent

Compd	N	Mean percent correct responses								
		0 h	1 h	2 h	4 h	8 h	1 day	2 days	3 days	4 days
2	5	96	80	38	32	40	57	95		
3	3	95	73	61	43	55	55	95	100	
4	3	97	63	70	75	93	87	98		
5	3	92	98	88	80	45	58	58	58	95
6	3	97	97	97	92	95	93			
Chlorpromazine	3	96	42	28	37	72	88	95		

activity recorded for compounds 2–5. We have seen that dichloro substituents on the phenyl ring of the benzoylpiperidine group reduce neuroleptic activity, as was evidenced by the lack of effect for compound 6. Of interest, however, was the unexpected long duration of action seen by compounds 2 and 5. With the exception of penfluridol, no other reference agent or experimental compound tested in these laboratories has been effective after 2 or 3 days, regardless of the dose employed. Various other procedures in animals have verified the potency and the long duration of action of compounds 2 and 5.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses for carbon, hydrogen, and nitrogen were determined using a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory except for compound 8 which was not purified. NMR (Varian Associates A-60 spectrometer) and mass spectral (Perkin-Elmer RMU-6H) data substantiate the structures given for compounds 2–6.

[1-[3-(2-Chlorophenothiazin-10-yl)propyl]piperidin-4-yl](4-fluorophenyl)methanone Fumarate (2). A mixture of 2-chlorophenothiazine (13.0 g, 0.055 mol), 1-(3-chloropropyl)-4-(4-fluorobenzoyl)piperidine (16.7 g, 0.059 mol), crushed potassium hydroxide pellets (16.8 g, 0.3 mol), and toluene (400 mL) was stirred at reflux temperature for 36 h. After standing 24 h at ambient temperature the mixture was filtered, and the filtrate was concentrated to yield 24.7 g of oil which appeared to be fairly pure on the bases of NMR and mass spectral analyses. The oil was distilled on a Büchi Kugelrohr apparatus at 250 °C (0.05 Torr). TLC analysis on silica gel (Analtech) in 5% methanol in chloroform showed the distillate to contain an impurity, R_f 0. The distillate was dissolved in $CHCl_3$ and filtered through a bed of Florisil in order to remove the polar impurity. The filtrate was concentrated to give 10.0 g of oil which was shown to be pure by TLC analysis. The fumarate salt was formed and recrystallized from methanol: yield 6.5 g (19.8%); mp 188–189 °C. Anal. ($C_{31}H_{30}N_2O_5FClS$) C, H, N.

[1-[3-(2-Chlorophenothiazin-10-yl)propyl]piperidin-4-yl](3,4-dichlorophenyl)methanone (6). A mixture of sodium bicarbonate (2.5 g, 0.03 mol), 10-(3-chloropropyl)-2-chlorophenothiazine (4.3 g, 0.014 mol), 4-(3,4-dichlorobenzoyl)piperidine hydrochloride (4.2 g, 0.043 mol), and 1-butanol (75 mL) was stirred at reflux temperature for 18 h. After cooling, the mixture was filtered and the filtrate concentrated at reduced pressure to yield 7.0 g of product. The hydrochloride salt was prepared but would not give a satisfactory elemental analysis. The free base was regenerated and crystallized on standing to yield 4.3 g of solid product (58%). The solid was recrystallized from benzene–isooctane twice: mp 143.5–145.5 °C. After drying at 110 °C for 16 h the material gave a satisfactory elemental analysis. Anal. ($C_{27}H_{25}N_2OCl_3S$) C, H, N.

2-Chloro-10-(3-chloropropyl)phenothiazine (8). A mixture of 2-chlorophenothiazine (32.2 g, 0.138 mol), 1-bromo-3-chloropropane (26.4 g, 0.168 mol), finely ground sodium hydroxide (27 g, 0.7 mol), and 500 mL of dimethylformamide was stirred for 3 h. The mixture was filtered and the filtrate concentrated. The residual oil was dissolved in isopropyl ether (500 mL) and filtered. The filtrate was concentrated and the residual oil dissolved in benzene to give 100 mL of solution. This solution was passed through a bed of Florisil in a 600-mL sintered glass Buchner funnel in four portions using benzene to elute the material, thus removing a polar component which was detected by TLC analysis on silica gel (Analtech) using 30% benzene in cyclohexane to develop the plate. The combined eluates were concentrated to yield 36.0 g of material consisting of 80% of compound 8 and 20% dehydrohalogenated material. The yield based on these percentages is 84%. The material was used in subsequent reactions without further purification.

4-(*p*-Fluorobenzoyl)-1-(3-hydroxypropyl)piperidine (10). A mixture of 4-(*p*-fluorobenzoyl)piperidine[1] (60.9 g, 0.293 mol), 3-bromopropanol (46.0 g, 0.31 mol), anhydrous potassium carbonate (41.4 g, 0.30 mol), and 1-butanol (750 mL) was stirred at reflux temperature for 15 h. After cooling, the mixture was filtered and the filtrate concentrated under vacuum. The residual oil was dissolved in dilute aqueous acid and extracted with benzene. The aqueous layer was basified and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and concentrated under vacuum. The residual oil crystallized on trituration in ether. The solid was collected by filtration and washed with ether yielding 57.0 g of product. Upon recrystallization from isopropyl ether–2-propanol, 38.5 g (48.5%) of product was obtained. A 4.0-g portion was recrystallized from petroleum ether to yield 2.4 g of solid crystalline product, mp 105–110 °C. Anal. ($C_{15}H_{20}FNO_2$) C, H, N.

[1-(3-Chloropropyl)-4-piperidinyl](4-fluorophenyl)-methanone (7). Thionyl chloride (38.7 g, 0.376 mol) was added dropwise to a stirred solution of 4-*p*-fluorobenzoyl-1-(3-hydroxy)propylpiperidine (43.1 g, 0.163 mol) in 400 mL of chloroform at room temperature. After the addition was complete, the reaction mixture was stirred at room temperature an additional 16 h. The mixture was then chilled and 125 mL of 6 N NaOH solution was added dropwise. The chloroform solution was separated, washed with water, and dried over magnesium sulfate. Removal of the solvent gave 42.7 g of crude product which crystallized on cooling. Recrystallization from isooctane gave 25.3 g (54.7%) of pure product, mp 66.5–68.5 °C. Anal. ($C_{15}H_{19}NOFCl$) C, H, N.

(3,4-Dichlorophenyl)(1-acetylpiperidin-4-yl)methanone (11). In a closed system *N*-acetylisonipecotic acid chloride (38.0 g, 0.2 mol) was added portionwise via a flexible connection to a stirred slurry of aluminum chloride (53.2 g, 0.4 mol) in o-dichlorobenzene (80 mL) at a rate such that the reaction temperature could be maintained at 5–10 °C. During the addition a total of 50 mL of methylene chloride was added as needed to facilitate stirring. After the addition was completed, the reaction mixture was stirred at room temperature for 2 days. The mixture was poured onto an excess of crushed ice and the resulting aqueous mixture extracted several times with chloroform. The chloroform extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The residual oil was triturated with isopropyl ether to induce crystallization, and 22 g of the solid product was collected (36.5% crude yield). A 5.0-g sample was recrystallized from acetone–water after treatment with charcoal. The off-white solid was then recrystallized from isopropyl ether–methanol: mp 134–136 °C. Anal. ($C_{14}H_{15}Cl_2NO_2$) C, H, N.

(3,4-Dichlorophenyl)(4-piperidinyl)methanone Hydrochloride (9). A mixture of 20 g (0.067 mol) of 1-acetyl-4-(3,4-dichlorobenzoyl)piperidine in 40 mL of 6 N HCl was stirred at reflux for 20 h. The mixture was cooled and made basic with 50% sodium hydroxide solution. The aqueous mixture was extracted several times with benzene, and the combined extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was dissolved in anhydrous ether and an excess of

ethereal HCl was added. The hydrochloride salt which precipitated was collected by filtration and air-dried. The solid weighed 10 g and upon recrystallization from 2-propanol–isopropyl ether gave 8.1 g (42%) of white solid, mp 205–208 °C. Anal. ($C_{12}H_{14}Cl_3NO$) C, H, N.

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3-Benzazocine Amidinium Nitronates. An Unusual Type of Opiate Antagonist

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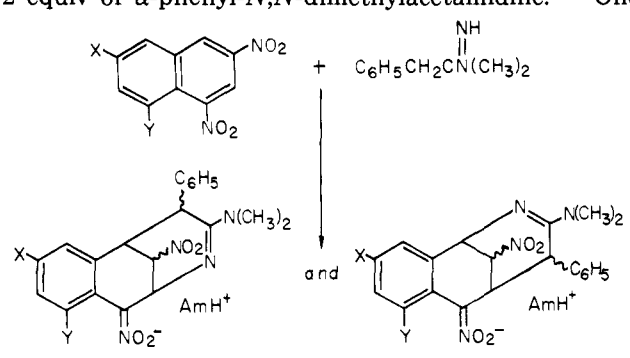
An interesting type of 3-benzazocine ring system which contains amidine functionality has been found to have significant narcotic antagonist activity. The isomeric 2-benzazocine, which incorporates similar structural features, except for the position of the ring nitrogen and adjacent phenyl substituent, is inactive. These 2- and 3-benzazocines can be synthesized in a single step from appropriately structured amidines and naphthalenes, and such syntheses may provide useful routes to new and interesting types of narcotic antagonists.

We recently reported the general synthesis and structure determination for a series of benzazocine amidinium nitronates prepared from 1,3-di- and 1,3,6,8-tetranitronaphthalenes.[1] We wish to report here the structure confirmation and pharmacological properties of certain isomeric 2- and 3-benzazocines in this series prepared from 1,3,6-trinitronaphthalene. A brief discussion of the interesting differences in activity between these isomers is presented. The 3-benzazocine amidinium nitronate may represent a new type of narcotic antagonist.

Two isomeric benzazocine amidinium nitronates (AmH^+ = α-phenyl-*N*,*N*-dimethylacetamidinium cation) **1** and **2** are formed by reaction of 1,3,6-trinitronaphthalene with 2 equiv of α-phenyl-*N*,*N*-dimethylacetamidine.[1] One



1, X = NO_2; Y = H
3, X = Y = NO_2

2, X = NO_2; Y = H
4, X = Y = H

isomer is obtained when the reaction is carried out in ethanol and the other is obtained when the reaction is carried out in Me_2SO.[1] When the reaction with 1,3,6,8-tetranitronaphthalene is carried out in Me_2SO, the 3-benzazocine **3** is formed, whereas with 1,3-dinitronaphthalene in Me_2SO the 2-benzazocine **4** is formed.[1] Using deuterium-labeled substrates the identity of **3** and **4** has previously been established.[1]

The structures of **1** and **2** are based solely on analogies with ^1H NMR chemical shifts for the di- and tetranitro analogues **3** and **4**. Confirmation of these assignments has now been obtained by deuterium labeling of the starting trinitronaphthalene, and the analgesic and analgesic–antagonist activity of **1–4** is reported here. We were specifically interested in the isomers **1** and **3** since the ring nitrogen and aromatic ring substituent are positioned similarly to those of frequently prepared pharmacologically active 3-benzazocines **5**.[2]

Pharmacological Results. Analgesia and analgesic–antagonism were measured using the mouse tail-flick test (see Experimental Section) as described by Harris and Dewey.[3] The antagonist screening results are summarized in Figure 1. The analgesic screening showed **1–4** all inactive. All were extremely insoluble and were administered intramuscularly or subcutaneously in Me_2SO.

The most definitive aspect of the data summarized in Figure 1 is the dose-related narcotic antagonism observed for **1** and the complete lack of activity (even at the high dose level of 20 mg/kg) for isomer **2** and the analogue **4**. This is evidence for a quite specific interaction resulting in narcotic antagonism from **1** and not a general CNS toxicity resulting from structures like **1–4**.

Interestingly, while **1** does contain the 3-benzazocine ring system, it also has a number of unusual structural features not associated with any previously reported narcotic antagonists. It is a nitronate salt with trigonal hybridization at C-1, analogous to ketazocine,[4] and the benzazocine nitrogen is trigonally hybridized in the form of amidine functionality. This ring nitrogen is unsubstituted and **1** does not contain a quaternary C-6 carbon. These latter structural features are usually found in benzazocine analgesics and analgesic–antagonists.[2]

The long delay in onset of maximum activity and extended duration of activity of **1** and **3** is probably related to slow absorption from the injection site. The extremely low solubility of these compounds in water makes it very likely that this factor is primarily responsible for the slow onset and sustained narcotic antagonism shown by **1** and **3**. The maximum antagonist activity occurs at about 8 h

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