Tab 2. Simulated concentration-time data obtained from formula [2] and analysis of results (FD / V = 100, $K = K_a = K_e = 0.5$).

n	Time	Concn	Concentration with 5% random error	A_i *
1	0.25	11.03	11.03	
2	0.5	19.47	20.44	0.199
3	1.0	30.33	28.81	0.647
4	2.0	36.79	36.79	0.422
5	4.0	27.07	25.72	0.512
6	6.0	14.94	15.69	0.447
7	8.0	7.33	7.70	0.499
8	10.0	3.37	3.54	0.500
9	12.0	1.49	1.42	0.548
10	16.0	0.27	0.28	0.477
11	20.0	0.05	0.05	0.486
12	24.0	0.01	0.01	0.448

* Calculation using formula[1] according to concentration with 5 % random error

误差后，在 c-t 曲线后段(从 6.0 计起)，各 A_i 值均与 0.5 近似，各 A_i 之算术平均值为 0.493，此值即为 K_a 与 K_e 值，与预定真值 0.5 的相对误差为 1.4%，证明[1]式及判定方法是正确的.

通过上述例证，说明本法是可行的.本法无需求出 c-t 曲线下面积(AUC)、达峰时(t_{max})和峰浓度(c_{max})，亦无需利用计算机进行非线性回归及通过作图法以判定 K_a 与 K_e 是否相等，且本法在判定 K_a 与 K_e 相等条件下，可较准确地计算出速率常数，故本法较为简便.本法为应用[2]或[9]式提供了一个依据.

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6β-乙酰氧基去甲托烷的毒蕈碱样受体动力学[1]

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6β-Acetoxy nortropane and its muscarinic receptor kinetics

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ABSTRACT Bao Gong Teng A (BGT-A), a cholinergic tropane, was first separated from *Erycibe obtusifolia* Benth in China in 1978. 6β-Acetoxy nortropane (6β-AN), a new tropane analogue of BGT-A, was synthesized in 1983, in our university. Tropanes are generally known as M-cholinoceptor blockers, but 6β-AN is a M-cholinoceptor agonist. The levorotatory 6β-AN is an active form that has been proved in biological and competitive binding test.

The receptor binding experiment of 6β-AN were compared with those of M-receptor agonists (oxotremorine, carbachol, BGT-A and

pilocarpine) and antagonists (pirenzepine, gallamine, atropine, scopolamine and anisodamine) on 4 different target tissues. The affinity order (pK_i) of 6β-AN to 4 tissues (heart,cortex-hippocampus, ileal longitudinal muscle and iris) were 7.7, 6.8, 5.6 and 5.5, respectively.

6β-AN improved performances of mice in three-arm maze. Down-step tests suggested some potential nootropic effect. 6β-AN decreased the heart rate and cardiac contraction, increased the ileal longitudinal muscle contraction and pupil constriction. All above mentioned biological effects were antagonized by atropine.

In receptor kinetics studies, we found marked discrepancy between pD_2 and pK_i. "The stronger the agonist, the larger the difference" suggest that different biological amplification systems are involved.

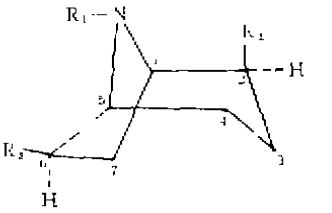
Study on the receptor regulation showed surprisingly a specific subtype receptor regulation and 6β-AN gave a downward regulation on M_2-R subtype only. Our data show that 6β-AN, gallamine, oxotremorine and carbachol are M_2-R subtype selective agents, while pirenzepine and pilocarpine are M_1-R subtype selective agents

KEY WORDS nortropanes; cholinergic receptors; heart; smooth muscles; ileum; iris; brain

提要 6β-乙酰氧基去甲托烷(6β-AN)是 M-乙酰胆碱受体(M-R)高亲和力激动剂，将它与传统 M-R 激动，拮抗剂对四种靶组织进行放射配体结合与生物活性试验，结果证明 pD_2 和 pK_i 之间差值与化合物的活性呈正比，6β-AN 对四种靶组织的亲和力次序是:心脏＞皮层海马＞肠纵肌＞虹膜.受体调节实验证明 6β-AN 属 M_2-R 亚型调节剂.

关键词 去甲托烷；胆碱能受体；心脏；平滑肌；回肠；虹膜；脑

包公藤甲素(Bao Gong Teng A, BGT-A)是我校姚天荣等首先从丁公藤(*Erycibe obtusifolia* Benth)中提出的生物碱，其化学名为 2β-羟基 6β-乙酰氧去甲托烷(2β-hydroxyl-6β-acetoxy-nortropane). BGT-A 为强效 M-R 激动剂，至今尚未见到有类似化合物的文献报道.由于植物中 BGT-A 含量太低，我校化学教研室根据其结构，合成多种托烷类似物，经生物活性测定，从中选出 6β-acetoxy nortropane (6β-AN)，在四种组织上进行生物活性、放射配体结合、受体调节等试验，进一步探讨此类化合物的受体动力学特点及其亚型受体调节.



Tropanes	R_1	R_2	R_3
Tropane	$-CH_3$	-H	-H
6β-Acetoxy nortropane (6β-AN)	-H	-H	-AcO
2β-Hydroxyl 6β-Acetoxy nortropane (BGT-A)	-H	-OH	-AcO

MATERIALS

New Zealand 兔 2.5 ± SD 0.4 kg ♂，昆明种小鼠 21 ± 3 g, ♂， Wistar 大鼠 204 ± 36 g, ♂，豚鼠 309 ± 50 g ♂，均由我校动物房供应.

[^{3}H] Quinuclidinyl benzilate ([^{3}H] QNB) 1.44 TBq / mmol Amersham England 产品；carbachol (Car), pilocarpine (Pil) 及 oxotremorine (Oxo) Sigma 产品；BGT-A 与 6β-AN 是我校化学教研室提供；scopolamine (Scop) 上海中医学院产品；pirenzepine (Pir) 上海第六制药厂赠送；anisodamine (Ani)杭州民生制药厂产品；gallamine (Gal) 法国 Specia 药厂产品；atropine (Atr)和 physostigmine (Phys) 均为生化试剂 AR.

METHODS AND RESULTS

6β-AN 旋光异构体的生物效应试验 从钝叶丁公藤提得的 BGT-A 是左旋体[1]，而人工合成的 BGT-A 是消旋体[2].6β-AN 经拆分

后所得的 3 个异构体 *l*-6β-AN, *d*-6β-AN 和 *dl*-6β-AN,分别进行兔在体缩瞳试验,虹膜括约肌膜受体与[^{3}H]QNB 竞争抑制试验，均证明其有效物是左旋体.兔在体缩瞳试验 *l*-6β-AN 与 *dl*-6β-AN 相比有显著差异，如 Tab 1 所示， *dl*-6β-AN 竞争抑制[^{3}H]QNB 所得的 IC_{50} 是 *l*-6β-AN 的两倍(Fig 1).

Tab 1. The pupil diameter (mm) of rabbits treated by 0.01 % *d*-, *dl*-, and *l*-6β-Acetoxy nortropane (6β-AN) as compared with the diameter (mm) pretreated. $n=5$, $\bar{x}\pm SD$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$.

Time (h)	*d*-6β-AN	*l*-6β-AN	*dl*-6β-AN
0.5	0.30±0.48*	−4.67±0.47**	−3.58±0.86**
1.0	−0.40±0.65*	−4.34±0.53***	−3.30±0.72***
2.0	−0.25±0.47*	−3.00±0.95**	−2.25±1.19*
4.0	0.40±0.49*	−0.94±0.41*	−0.40±0.42*
Salivation	0/5	5/55	1/5
Defecation	0/5	3/5	2/5

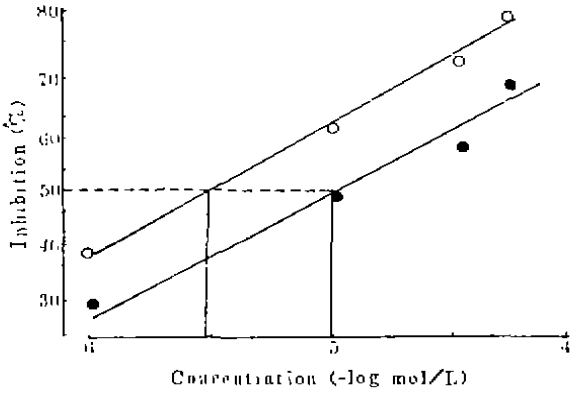


Fig 1. Competition binding assay of *dl*-6β-AN(●), *l*-6β-AN(○) *vs* [^{3}H]quinuclidinyl benzilate.

中枢 M-R 动力学研究

1 慢性埋藏电极兔 3 只,记录脑电(EEG)[3]后，用 M-R 拮抗剂 Scop 0.02 mg/kg iv，即刻使脑电产生高幅慢波，可维持 90 min.给药 20 min 后用 Phys 0.2 mg/kg iv 或 6β-AN 12 μg/kg iv，即刻记录 EEG，数据经积分值处理[3]，6β-AN 与 Phys 均能对抗 Scop 的高幅慢波，其等效克分子比 6β-AN:Phys 为 1:12 (待发表资料).

2 小鼠迷宫、跳台试验[4] 小鼠 160 只，每组 10 只，分别 ip 6β-AN 和 Phys 各 3 个剂量组 0.08, 0.10, 0.12 mg/kg, 24 h 后进行迷宫、跳台测试，用等容量 NS 作对照.6β-AN 和 Phys 组，均能促进学习记忆功能，显示典型的倒"U"量-效关系(Fig 2).

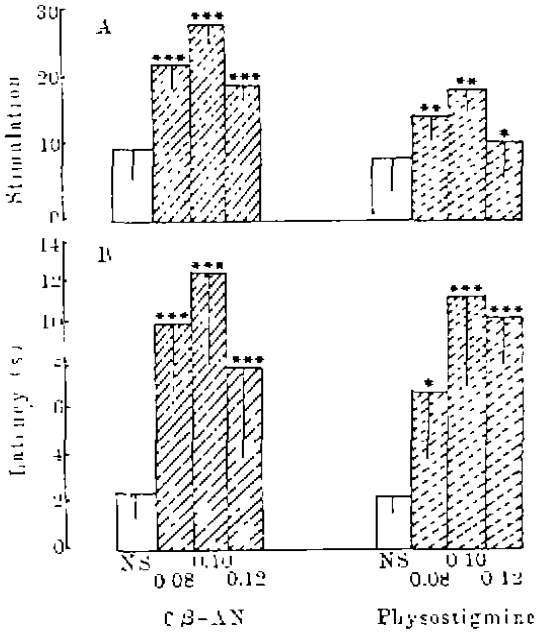


Fig 2. (A) Number of stimulations (three-arm Y maze method) (B) step-down latency(s) (step-down test method) by ip 6β-AN and Physostigmine *vs* NS. $n=10$, $\bar{x}\pm SD$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$.

3 大鼠皮层海马区膜受体对[^{3}H]QNB 的竞争抑制结合试验[5] 分别采用 M-R 激动剂 6β-AN, Oxo, Pil, Car, 拮抗剂 Pir, Gal, 测得竞争抑制参数 p*K*i(受体亲和强度)次序为 Pir>Oxo>Gal> Pil≥ 6β-AN > Car, 等效克分子, Pir:Gal 的亲和力比为 28:1(Tab 2).

外周组织 M-R 动力学研究

1 豚鼠心脏 *M-R* 生物效应测试 离体豚鼠左心房，置于通有 95%O_2+5%CO_2 水浴槽内，温度控制在 32℃，联接 JL-3 三通生理

Tab 2. pK_i values of 6β-AN, pilocarpine (Pil), carbachol (Car) oxotremorine (Oxo),pirenzepine (Pir), and gallamine(Gal) in the displacement [^{3}H]QNB binding assay on rat brain and heart M-receptors. $n=3$, $\bar{x} \pm SD$.

Drug	Brain pK_i	*b	Heart pK_i	*b
6β-AN	6.38±0.05	1.0571±0.002	7.95±0.00	0.9423±0.01
Pil	6.50±0.04	0.9073±0.001	6.51±0.01	0.9191±0.10
Car	5.90±0.04	1.3413±0.050	7.14±0.01	1.2090±0.04
Oxo	7.59±0.01	1.0591±0.007	7.89±0.00	0.9269±0.01
Pir	8.12±0.00	1.0420±0.050	6.76±0.02	0.9614±0.08
Gal	6.67±0.02	1.0176±0.100	7.87±0.00	1.0127±0.01

*b = Slope Scott's regression formula

记录仪，连续记录心房的收缩力及频率.然后分别用 M-R 激动剂 6β-AN，Oxo，Car 观察上述两指标的变化，三药均能使离体豚鼠心房肌的收缩力和收缩频率减少，并表现出剂量依赖性，三者的 pD_2 一致表现为收缩力 > 频率(Tab 3).用 Pir 或 Gal 都能取消三药的作用.抗频率和收缩力之间的剂量无明显差异(Tab 4).

Tab 3. pD_2 values of 6β-AN, Oxo and Car on inotropy (Ino) and chronotropy (Chro). $n=5$, $\bar{x} \pm SD$.

Drug	pD_2 Inotropy	pD_2 Chronotropy	Antilog pD_2(Ino)-pD_2(Chro)
6β-AN	8.61±0.00	7.78±0.01	6.8
Oxo	8.88±0.00	8.21±0.00	4.7
Car	7.75±0.01	6.61±0.03	7.8

Tab 4. pA_2 values of Gal and Pir for 6β-AN, Oxo and Car on inotropy and chronotropy of guinea pig heart.

Antago / Ago	n	Inotropy	Chronotropy
Pir / 6β-AN	3	6.20±0.06	5.85±0.39
Pir / Oxo	4	6.94±0.58	6.77±0.42
Pir / Car	4	5.83±1.04	5.96±0.74
Gal / 6β-AN	4	6.03±0.63	6.02±0.04
Gal / Oxo	3	5.84±0.27	5.85±0.33
Gal / Car	4	5.91±0.16	5.90±0.42

2 豚鼠心房肌细胞内微电极动作电位研究试验[6] 6β-AN 和 Car 对细胞内微电极引导的动作电位时程(APD)有抑制作用，并能明显缩短有效不应期(ERP).两药抑制 APD_{90} 的复极作用尤为明显，6β-AN 对 APD_{90} 的抑制强度比 Car 约大两个数量级(Fig 3).随着 6β-AN 的剂量由 0.048 μmol / L 增加至 0.48 μmol / L，Pir 对抗 6β-AN 抑制 APD 的作用消失(Tab 5).

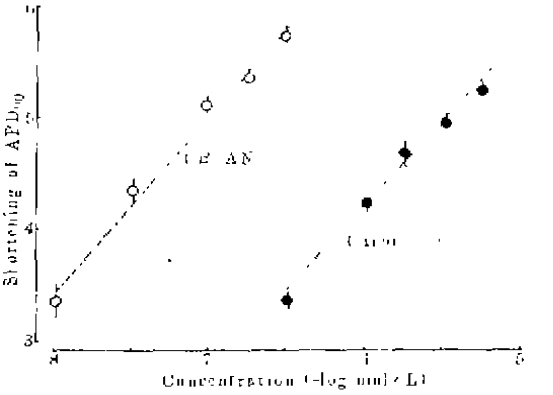


Fig 3. Dose response curve of shortening of 90% action potential duration (APD_{90}) by 6β-AN and carbachol.

3 心房膜受体的[^{3}H]QNB 竞争抑制结合试验 方法同皮层海马区的结合试验，用激动剂 6β-AN，Oxo，Pil 及 Car，拮抗剂 Pir 及 Gal，测得亲和力强度次序为:6β-AN > Oxo ≥ Gal > Car > Pir > Pil. Gal 和 Pir 的 pK_i 分别为 7.87，6.76，故 Gal 对心脏膜受体的亲和力比 Pir 强 13 倍(Tab 2).

4 兔虹膜括约肌生物效应测试[7] 6β-AN、BGT-A 与 Pil 对兔在体缩瞳及兔离体虹膜累加剂量效应测得的 $pD_{2(p)}$(在体缩瞳 pD_2)及 $pD_{2(i)}$(离体虹膜 pD_2)，其强度次序

Tab 5. Antagonism of large dose of 6β-AN on the transmembrane action potentials of guinea pig atria induced by Pir. $n=3$, $\bar{x}\pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* Pir or control.

parameter	Control	Pir	6β-AN	
		1.8μmol / L	0.048 μmol / L	0.48 μmol / L
RP	98.6±3.1	95.4±3.3	96.1±2.9	96.7±3.1*
APA	128.0±5.7	127.9±4.7	127.1±5.6	128.6±6.1*
V_{max}	273.0±32.5	270.5±31.4	274.5±30.2	281.0±32.7*
APD_{20}	22.0±3.8	25.2±6.5	26.4±5.3	16.8±4.5**
APD_{50}	42.5±6.6	49.6±10.2	47.9±11.2	30.3±10.9**
APD_{90}	74.0±14.4	75.9±15.4	72.4±12.6	41.2±11.7***
ERP	68.9±21.5	76.2±9.1	74.7±18.4	44.8±16.3**

一致表现为 6β-AN > BGT-A > Pil，然而 6β-AN 的 $pD_{2(p)}$ 与 $pD_{2(i)}$ 分别为 6.8 和 6.9.但 BGT-A 和 Pil 两药的 $pD_{2(p)}$ 与 $pD_{2(i)}$ 之间的差值颇为显著(Tab 6).从化学结构角度分析，在托烷母核上，BGT-A 比 6β-AN 多一个羟基，影响了它对生物膜的穿透能力，Pil 除了它对生物膜穿透力弱外，它还是一个弱的 M-R 激动剂(待发表资料).

Tab 6. pD_2(pupil) pD_2 (iris) and pK_i values of 6β-AN, BGT-A, and Pil on the rabbits pupil, iris and membrane receptors. $n=7$, $\bar{x}\pm SD$.

Drug	6β-AN	BGT-A	Pil
pD_2 (pupil)	6.83±0.05	5.62±0.05	4.08±0.13
pD_2 (iris)	6.92±0.01	6.12±0.12	5.41±0.38
pK_i	5.49±0.06	4.69±0.56	5.10±0.19
Antilog $pD_2(i)-pK_i$	27	27	2

5 兔虹膜受体[³H]QNB 竞争抑制结合试验 膜受体的提取实验方法同肠纵长肌，分别测得 6β-AN，BGT-A 与 Pil 的 pK_i，pD_2.三药的 $pD_{2(i)} > pK_i$，说明产生效应只需占领一部分受体，而高效能药物更为明显，由于 $pD_{2(i)}$ 与 pK_i 差值与化合物的活性呈正比，推测高生物活性的激动剂在受体后，有强大的生物放大系统参与(Tab 6).

6 豚鼠肠纵长肌生物效应与膜受体[³H]QNB 竞争结合抑制试验[8] 测得各化合物的 pK_i 值次序为 Scop > Atr > Ani > Oxo ≥ 6β-AN > BGT-A ≥ Pil. pD_2 的次序为 6β-AN > Oxo > BGT-A > Pil，在 pD_2 和 pK_i 差值同样表现与激动剂的生物活性呈正比.在用 Atr 对抗 6β-AN，BGT-A 及 Pil 的实验中，分别测得 Atr 对抗 3 个药物的 pA_2 分别为 9.1，8.7，8.1(未发表资料)，从 Tab 7 中 Atr 的 pK_i 为 8.0 和 Atr 抗 Pil 的 pA_2 为 8.1，两值非常接近，可以推测低效能的 pil 必需占领极大部分的受体后，才能产生效应.

Tab 7. pD_2 and pK_i values of 6β-AN, BGT-A, Oxo, Pil, Atr, Scop and Ani on Ileum longitudinal muscle. $n=7$, $\bar{x}\pm SD$.

Drug	pD_2	pK_i	Antilog pD_2-pK_i
6β-AN	7.72±0.01	5.62±0.04	125.9
BGT-A	6.51±0.09	4.94±0.47	37.2
Oxo	7.29±0.01	5.77±0.04	33.1
Pil	5.83±0.03	4.72±0.47	12.6
Atr		8.01±0.04	
Scop		8.54±0.07	
Ani		7.01±0.06	

综合以上 4 种靶膜受体(心脏、皮层海马区、肠纵长肌、虹膜)，6β-AN 抑制[³H]QNB 的 pK_i 次序是 7.95 > 6.38 > 5.6 ≥ 5.5. 提示 6β-AN 对心脏膜受体的亲和力最大(Tab 8).

受体的调节作用 用 M-R 激动剂，拮抗剂 6β-AN，Oxo，Scop 对大鼠皮层海马区 M_1-R 及心脏组织 M_2-R 的调节实验. 大鼠 sc 6β-AN 2 mg/kg bid，Oxo 0.5 mg/kg bid，Scop

Tab 9. Regulation of the M-receptors of rat cerebral cortex-hippocampus, heart by 6β-AN, Oxo and Scop. pK_D (-log dissociation constant). $n=7$, $\bar{x}\pm SD$. $^*P>0.05$, $^{**}P<0.05$ *vs* NS.

Treatment	Cortex-hippocampus		Heart	
	pK_D	B_{max}(pmol/mg)	pK_D	B_{max}(pmol/mg)
NS	10.32±0.02	0.4860±0.175	10.68±0.01	0.0669±0.015
6β-AN	10.19±0.02	0.4556±0.175*	10.62±0.02	0.0561±0.012**
Oxo	10.24±0.01	0.3895±0.149**	10.64±0.01	0.0469±0.015**
Scop	10.16±0.01	0.5796±0.178**	10.72±0.01	0.0674±0.024*

Tab 8. pK_i values of 6β-AN *vs* [^{3}H]QNB on cerebral cortex and hippocampus, heart, ileum longitudinal muscle (LM) and pupil. $n=3$, $\bar{x}\pm SD$.

Cortex-hippo (rat)	pK_i	b
Cortex-hippo(rat)	6.38±0.05	1.057±0.002
Heart(rat)	7.59±0.00	0.942±0.009
LM(guinea pig)	5.62±0.08	1.160±0.064
Pupil(rabbit)	5.49±0.05	1.160±0.100

12 mg/kg qd, NS 等容量作对照，连续给药 10 d，停药 24 h 后，迅速取出皮层海马区与心脏组织，提取膜受体(方法同前).用[^{3}H]QNB 对膜受体进行结合试验，经 Scatchard 公式处理得 pK_D 与 B_{max}. 结果如 Tab 9 所示.

DISCUSSION

本文对 2 个具有托烷类结构的 M-R 激动剂，进行中枢与外周 4 种不同靶组织的受体动力学研究，证明 6β-AN 是一个强的 M-R 激动剂.

6β-AN 对促进学习记忆需有一最佳剂量，过大或过小均不利突触兴奋的信息传递[9].6β-AN 和 Car 对心脏的生物活性作用，表现为收缩力>频率，上述作用均可被 Pir 或 Gal 对抗，2 拮抗剂的剂量在抗收缩力与频率方面无明显差别.作者并未发现在心脏上存在着亚型受体的调节[10];并支持 M-激动剂对负性肌力与负性频率作用的差别，是由于心脏的不同区域，受体密度和胆碱酯酶活性差异所致的论点[11].

本文发现，无论在膜受体结合试验中，或亚型受体调节试验中，6β-AN 均表现对心脏的 M_2-R 有较大的亲和力，而 Scop 对受体的调节作用[12]与 6β-AN 相反，对外周平滑肌 M-R 动力学参数一致表现为 $pD_2>pK_i$，且 2 参数的差值与激动剂的生物活性呈正比，而拮抗剂则否.从而证明，不同生物活性的激动剂结合受体后，可能触发不同的生物放大系统.

最后在 Fig 4 中，作者以皮层海马区的 pK_i 对心脏 pK_i 作图，证明 6β-AN,Car 和 Gal 是 M_2-R 选择性化合物;Pir 是 M_1-R 选择性化合物.至于 Oxo 和 Pil 有文献报道[13, 14]，前者倾向选择作用在 M_2-R 后者选择作用于 M_1-R.我们的结果支持这种分类方法.

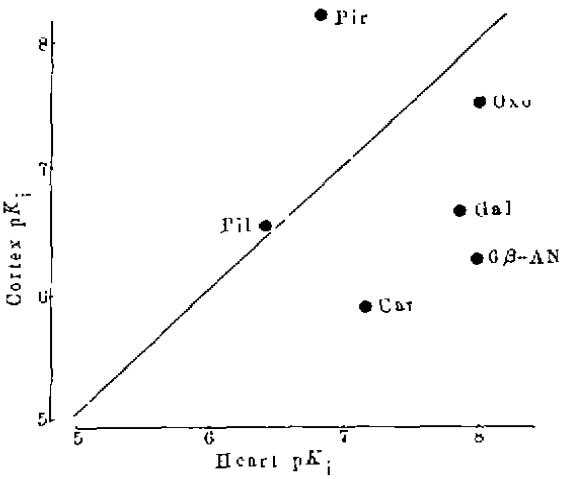


Fig 4. The pK_i of M-receptor drugs 6β-AN, Oxo, Pil, Car, Gal and Pir on cortex-hippocampus *vs* heart.

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模糊聚类法分析头孢菌素结构及其免疫交叉反应的关系

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Fuzzy cluster for analysis of the relationship between the structure of cephalosporins and immune cross-reaction

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ABSTRACT Six parameters (molecular negentropy, acidic group number, basic group number, proton donor group number, proton acceptor group number, and a ratio of C atomic group number to total atomic group number) for characterizing the structure of an antibody combining site in a R_1 chain of cephalosporins were selected. Although 12 parameters characterized the site A and site B in a R_1 chain were used in fuzzy cluster, Fischer weighting ratio (Fi) indicated that only 5 parameters, 4 of them characterized the structure of site A, play an important part in the cluster. Therefore it was speculated