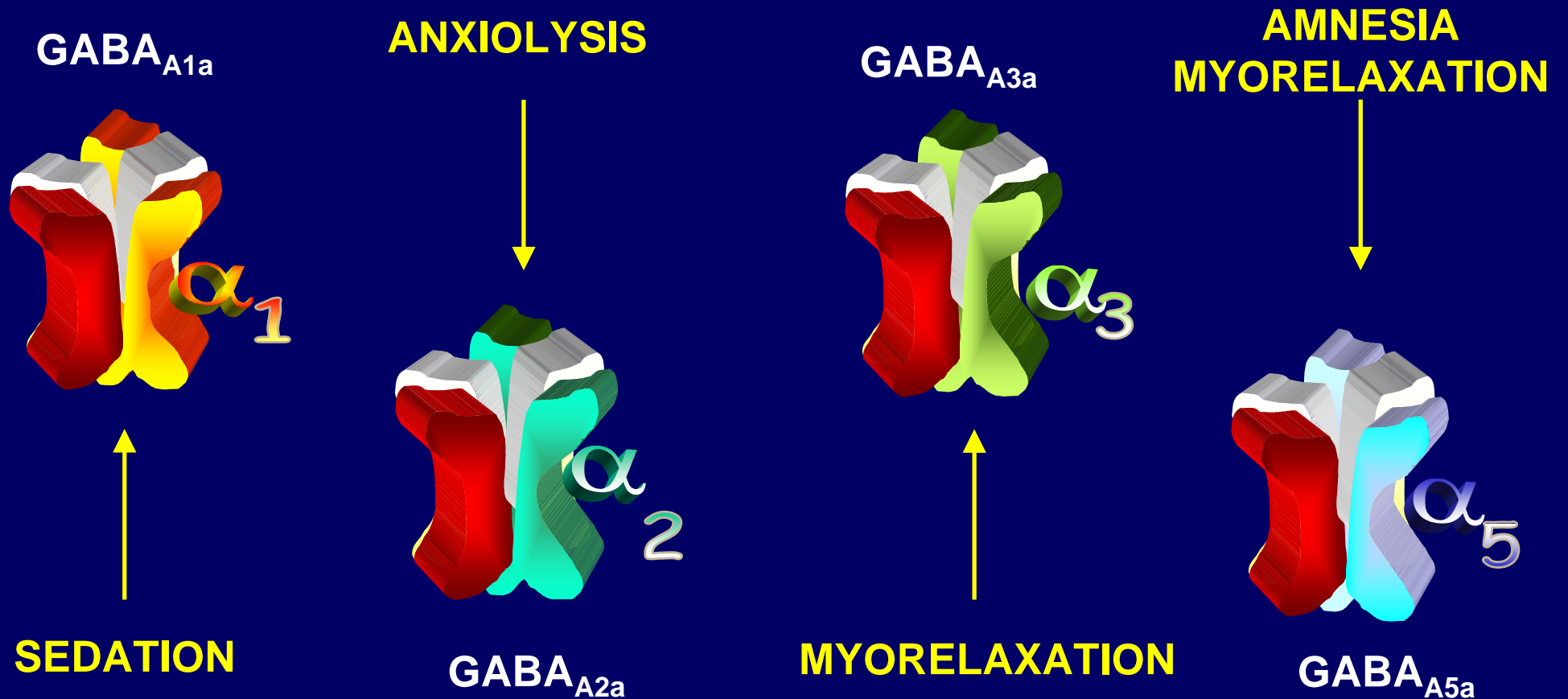


SL651498:
A NEW ANXIOLYTIC WITH
FUNCTIONAL SELECTIVITY
FOR GABA_{A2a} AND GABA_{A3a}
RECEPTOR SUBTYPES

MAIN FUNCTIONS OF GABA_A RECEPTOR SUBTYPES



Based on Löw et al., 2000; McKernan et al., 1999; Rudolph et al., 1999

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PROFILE EXPECTED FOR AN ANXIO-SELECTIVE GABA_A RECEPTOR LIGAND

↙ High affinity and intrinsic efficacy at the
GABA_A α₂ subtype

↙ Weak affinity and/or low intrinsic efficacy at
GABA_A α₁, α₃ and α₅ subtypes

SL651498



6-Fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-yl-carbonyl)-2,9-dihydro-1H-pyrido [3,4-b] indol-1-one

Patent: FR-9612229 (10/8/96) & PCT/FR97/01750 (10/3/97)

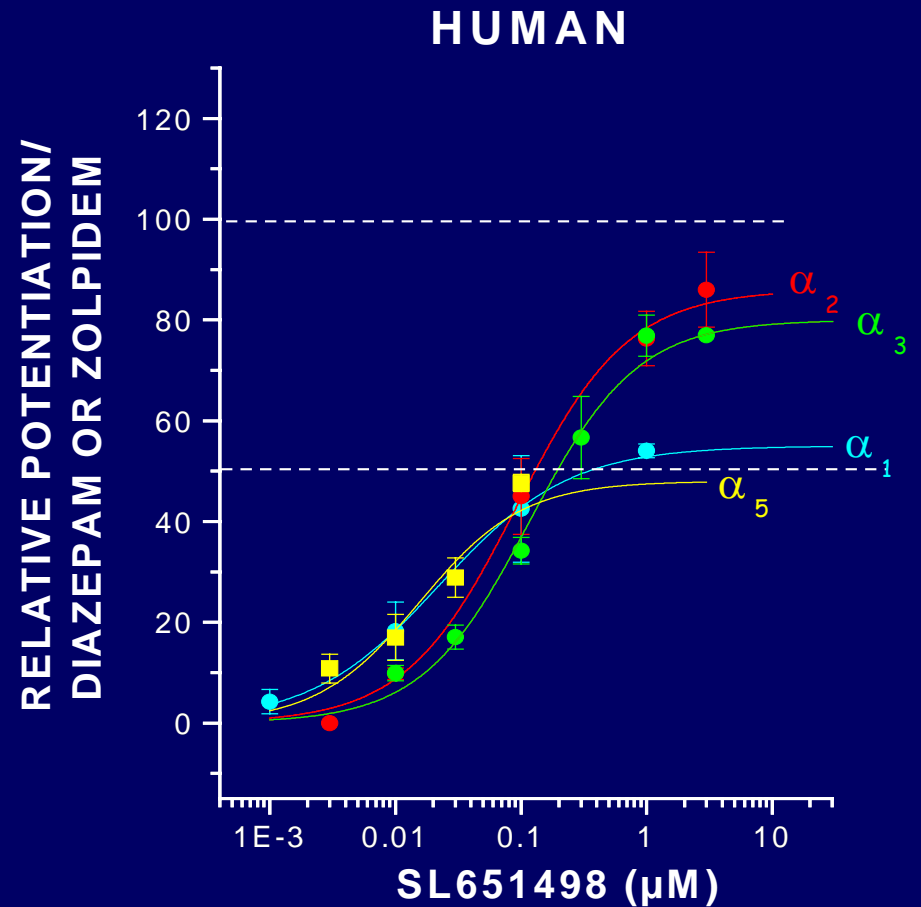
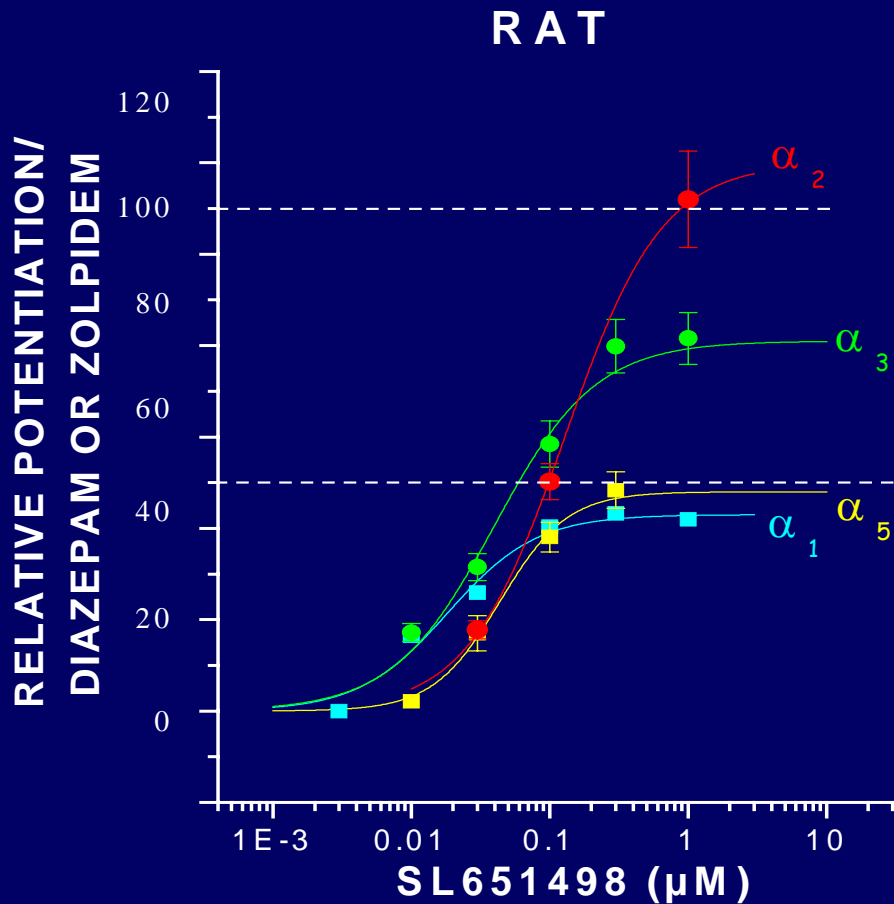
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IN VITRO BINDING PROFILE AT GABA_A RECEPTOR SUBTYPES

	CI ₅₀ , nM			
	$\alpha_1\beta_2\gamma_2$	α_2 -native	$\alpha_3\beta_2\gamma_2$	α_5 -native
SL651498	14	38	207	450
Diazepam	17	14	57	51

$$\alpha_1 = \alpha_2 > \alpha_3 > \alpha_5$$

GABA-INDUCED Cl⁻ CURRENTS POTENTIATION BY SL651498 RELATIVE TO ZOLPIDEM (α_1) OR DIAZEPAM ($\alpha_2, \alpha_3, \alpha_5$) IN HEK293 CELLS STABLY EXPRESSING GABA_A RECEPTOR SUBTYPES



Partial agonist at α_1 and α_5 , full agonist at α_2 and α_3

ANXIETY MODELS USED

CONFLICT TESTS

- PUNISHED LEVER PRESSING
- VOGEL



EXPLORATION TESTS

- ELEVATED PLUS-MAZE
- 4-PLATE
- LIGHT/DARK



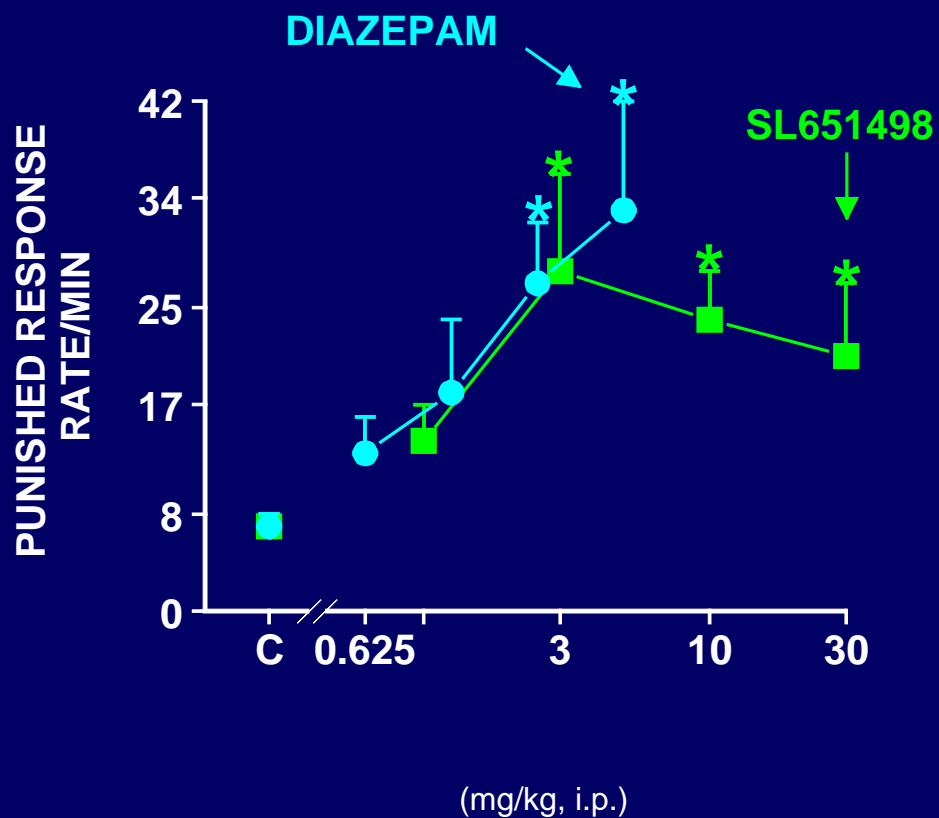
DEFENSIVE BEHAVIORS

- MOUSE DEFENSE TEST BATTERY

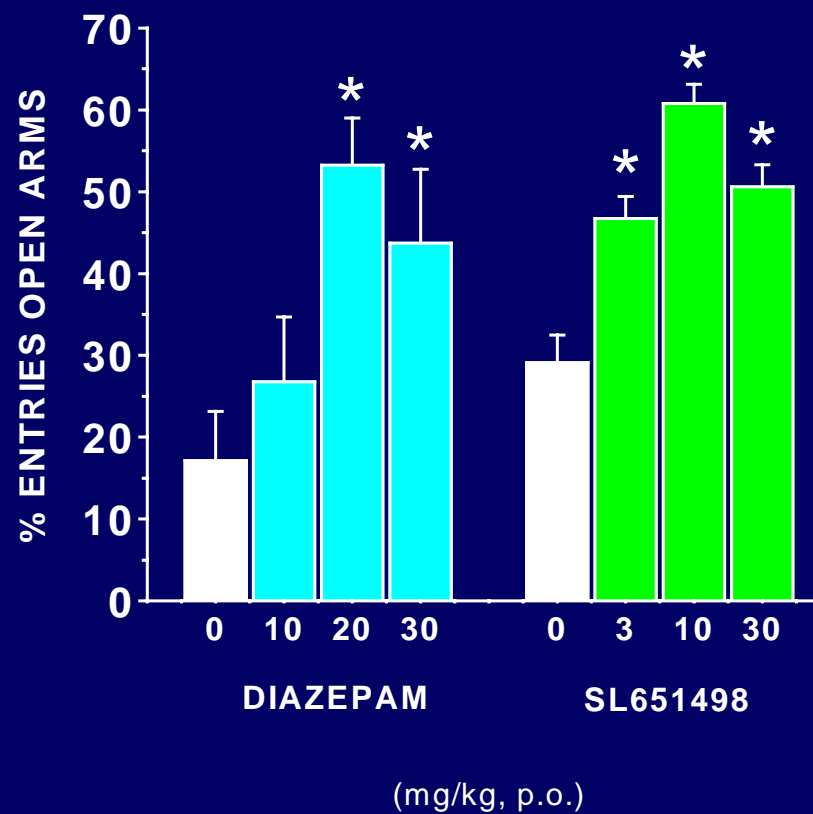


ANXIOLYTIC-LIKE ACTIVITY OF SL651498 IN RATS

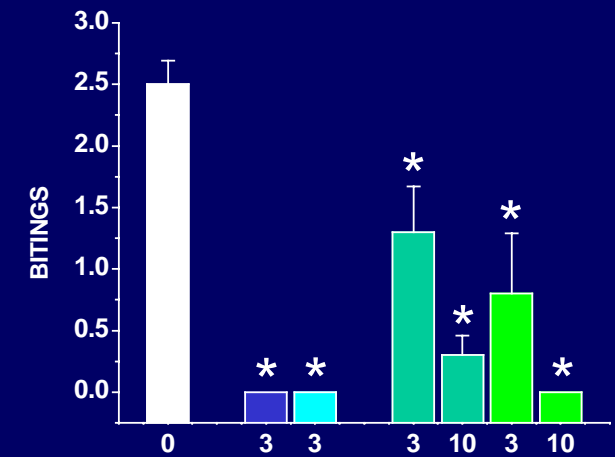
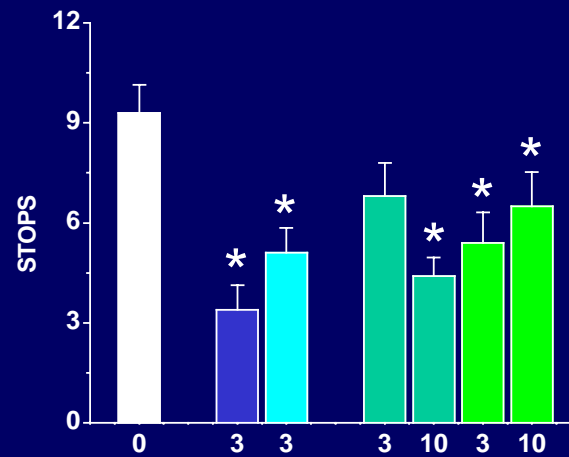
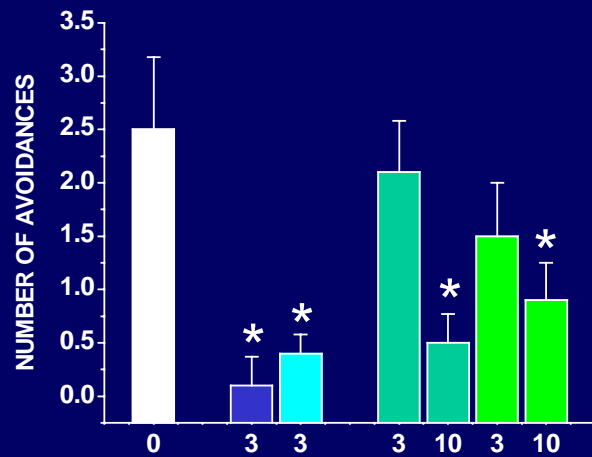
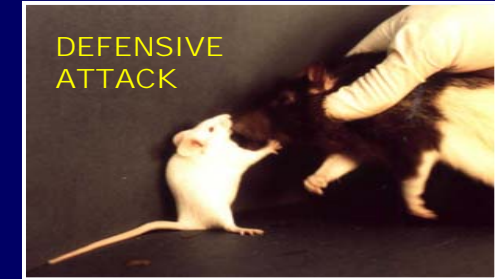
PUNISHED LEVER PRESSING



ELEVATED PLUS-MAZE



ANXIOLYTIC-LIKE ACTIVITY IN THE MOUSE DEFENSE TEST BATTERY



DIAZEPAM ACUTE
 SL651498 ACUTE
 DIAZEPAM REPEATED
 SL651498 REPEATED (14 days/bid)

(mg/kg, p.o.)

COMPARISON OF THE ANXIOLYTIC-LIKE EFFECTS OF SL651498 WITH THOSE OF OTHER ANXIOLYTICS

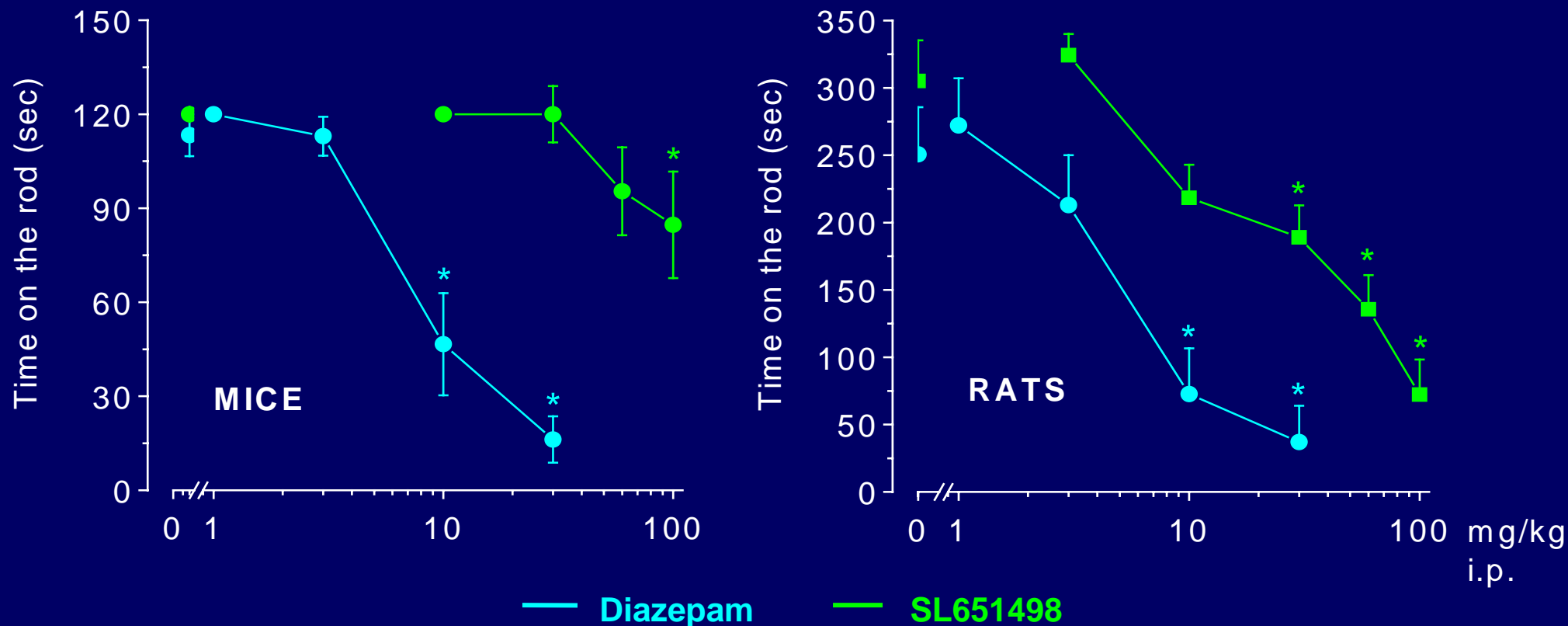
MINIMAL EFFECTIVE DOSE, mg/kg, ip (po)

	Punished Lever	Rat			Mouse	
		Vogel	Plus-maze	MDTB	Light/dark	4-Plate
SL651498	3	10 (10)	1 (3)	3 (3)	10	4
Diazepam	2.5	1 (10)	1.5 (20)	3 (3)	2.5	2.5
Bretazenil	1	1	0.03	10	30	
Buspirone	>2.5	2.5	>4	1.25	>15	(>100)

MAIN SIDE-EFFECTS ASSOCIATED WITH THE USE OF BENZODIAZEPINES

- **Ataxia**
- **Myorelaxation**
- **Sedation**
- **Interaction with alcohol**
- **Amnesia**
- **Physical dependence**

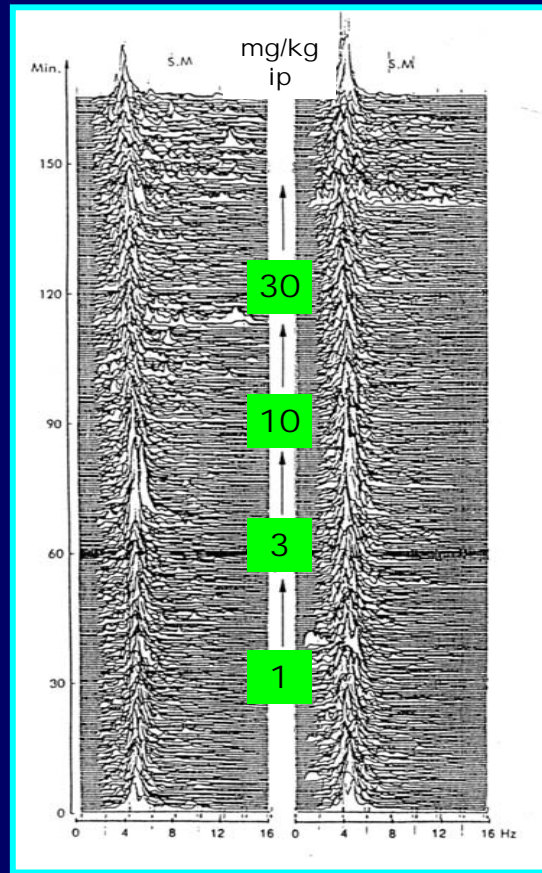
EVALUATION OF THE ATAXIC EFFECTS OF SL651498 IN THE ROTAROD TEST



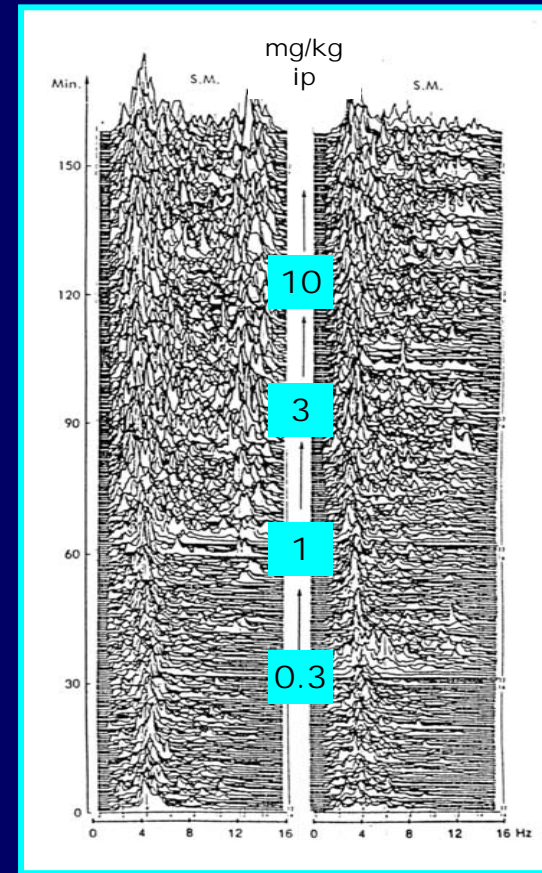
SL651498 does not produce ataxia up to 100 mg/kg (mice) and 30 mg/kg (rat), ip

EVALUATION OF THE SEDATIVE PROPERTIES OF SL651498 AS MEASURED BY EEG IN RATS

SL651498



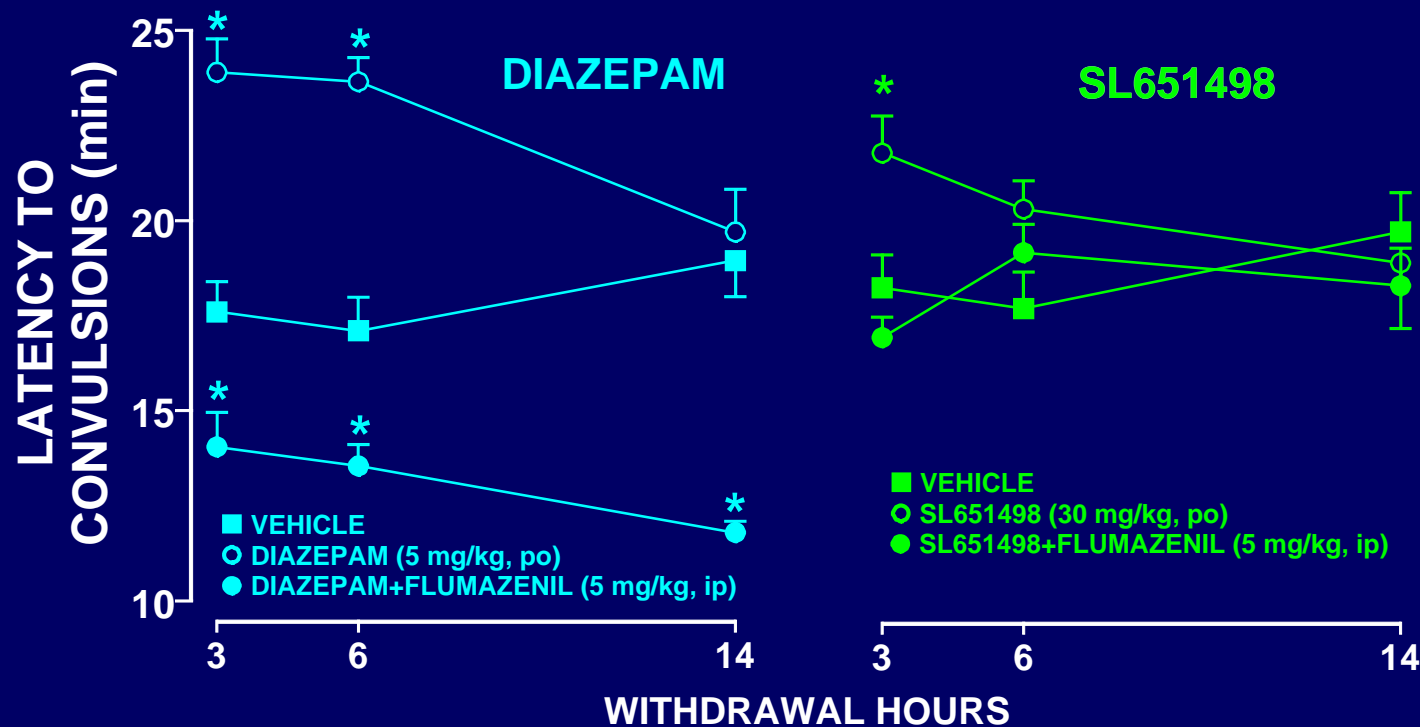
DIAZEPAM



SL651498 does not produce significant sedative effects up to 30 mg/kg (ip)

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EVALUATION OF THE PROPENSITY TO PRODUCE SIGNS OF WITHDRAWALS FOLLOWING ABRUPT DISCONTINUATION OF REPEATED ADMINISTRATION (10 d/bid) IN THE ISONIAZID-INDUCED CONVULSION TEST IN MICE



SL651498 does not produce signs of withdrawal following abrupt discontinuation

PHARMACOLOGICAL PROPERTIES

High affinity for the GABA_A α_2 subtype

- Active in classical animal models of anxiety



EXPECTED CLINICAL PROFILE

Efficacy in general anxiety disorder

Partial agonist at the GABA_A α_1 subtype

- No sedation
- Lack of potentiation of the loss of righting reflex induced by ethanol and barbital at anxiolytic doses



Wide separation between anxiolytic effects and sedation



Weak potential of interaction with central depressant drugs

Partial agonist at the GABA_A α_5 subtype

- No impairment on spatial memory task in rats
- Lack of precipitated withdrawal signs after repeated treatment
- Ataxic and myorelaxant effects appear at high doses only



Low propensity to induce cognitive impairment



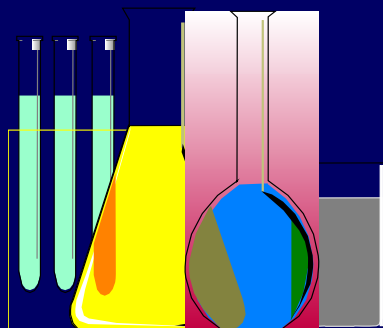
Low liability to induce physical dependence



Wide separation between anxiolytic and motor effects

SL651498

CHEMISTRY



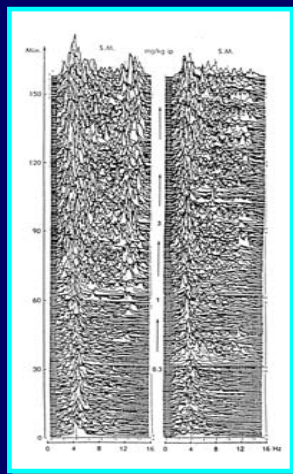
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