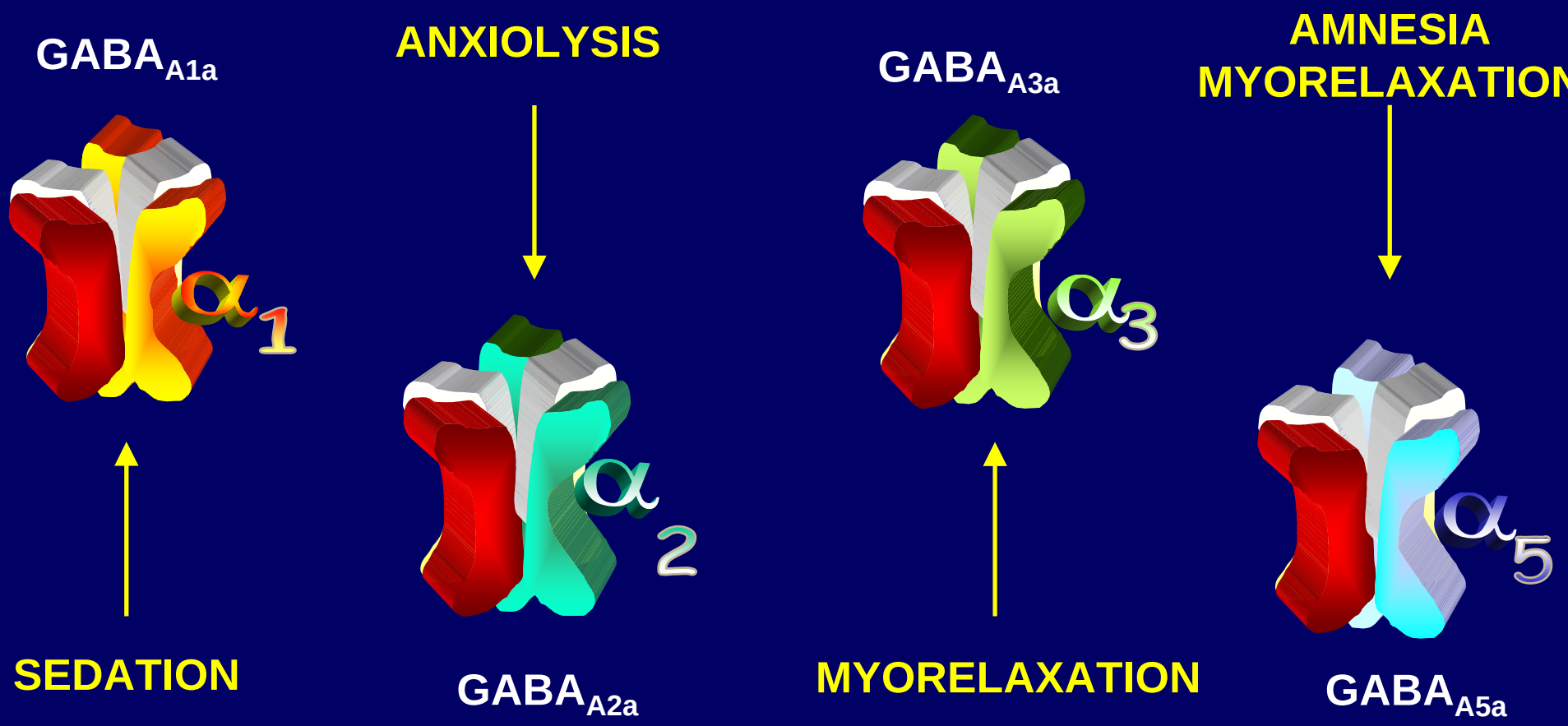
SL651498:

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 $GABA_A$ α_2 subtype**
- **Weak affinity and/or low intrinsic efficacy at $GABA_A$ α_1, α_3 and α_5 subtypes**

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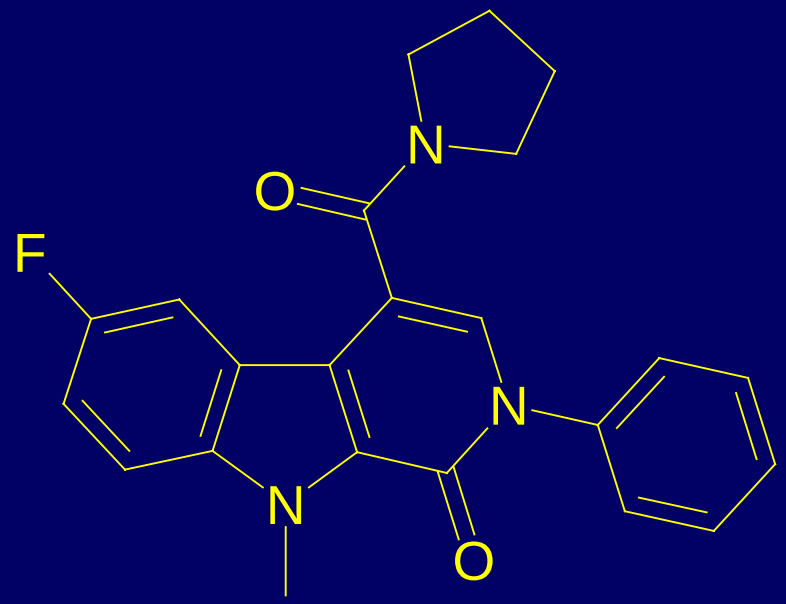

6-Fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-yl-carbonyl)-2,9-dihydro-1*H*-pyrido [3,4-*b*] indol-1-one

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

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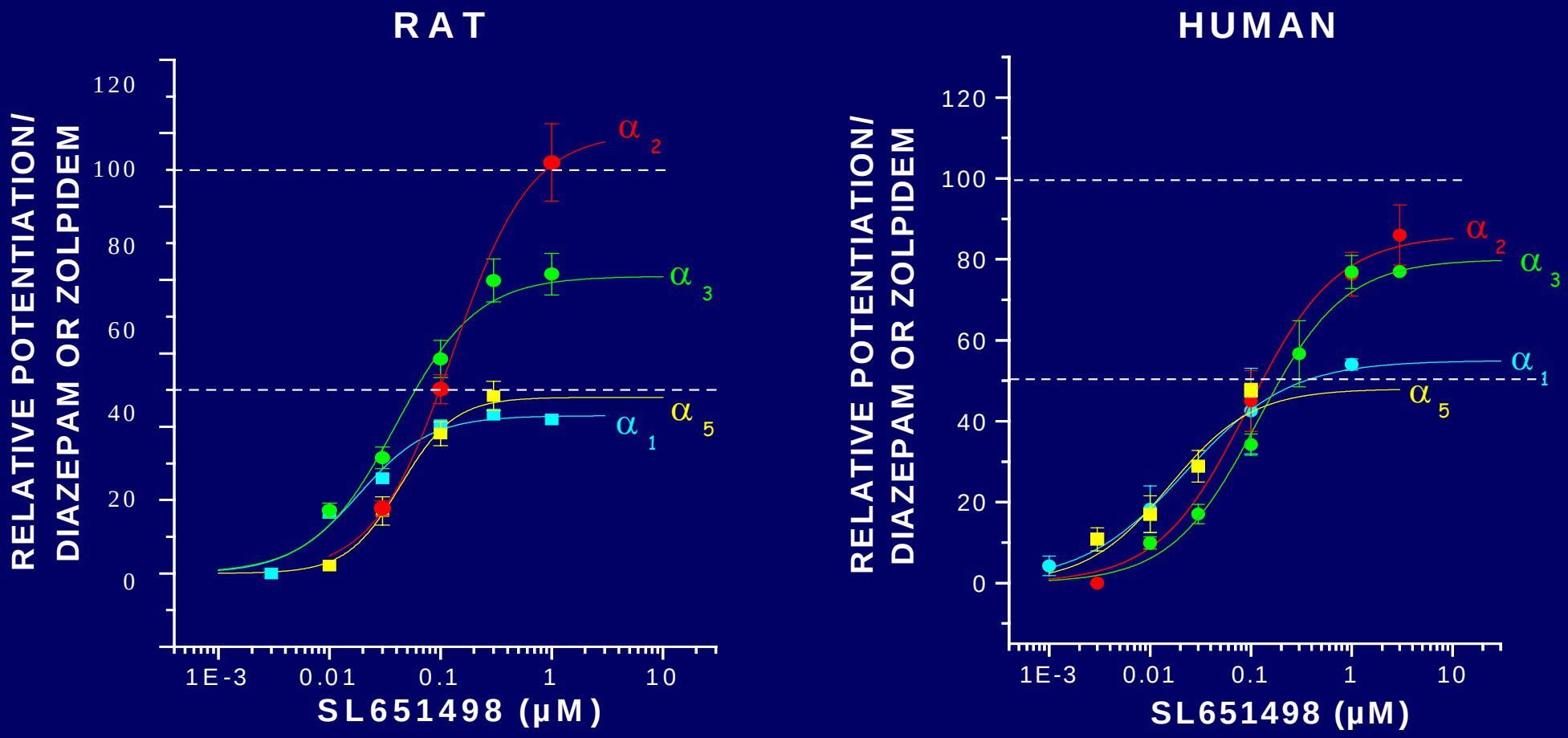
IN VITRO BINDING PROFILE AT $GABA_A$ RECEPTOR SUBTYPES

	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 (α_2, α_3, α_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

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ANXIETY MODELS USED

CONFLICT TESTS

- PUNISHED LEVER PRESSING
- VOGEL

EXPLORATION TESTS

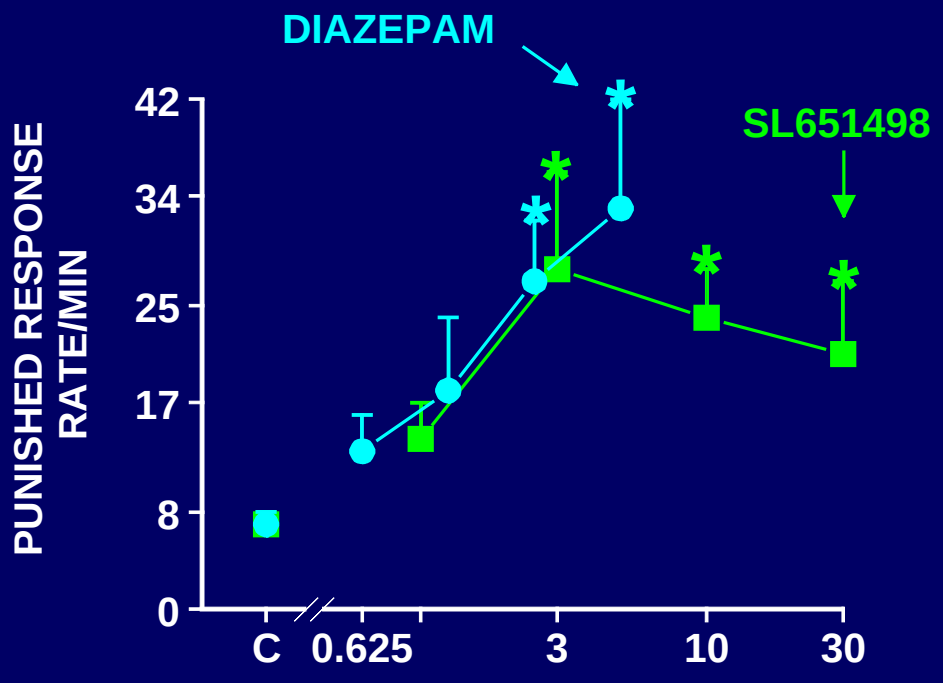
- ELEVATED PLUS-MAZE
- 4-PLATE
- LIGHT/DARK

DEFENSIVE BEHAVIORS

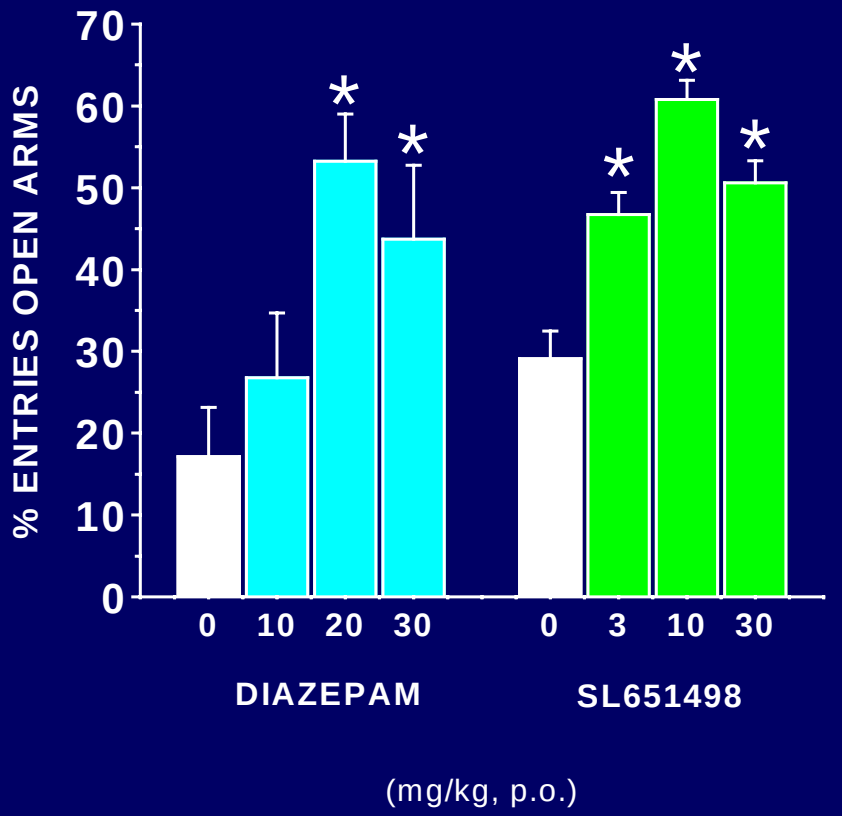
- MOUSE DEFENSE TEST BATTERY

ANXIOLYTIC-LIKE ACTIVITY OF SL651498 IN RATS

PUNISHED LEVER PRESSING



ELEVATED PLUS-MAZE



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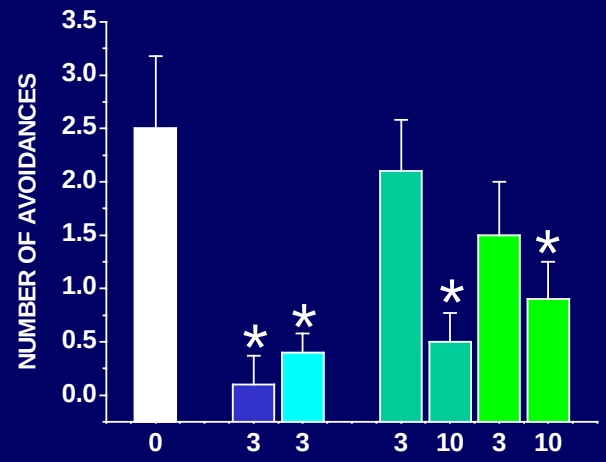
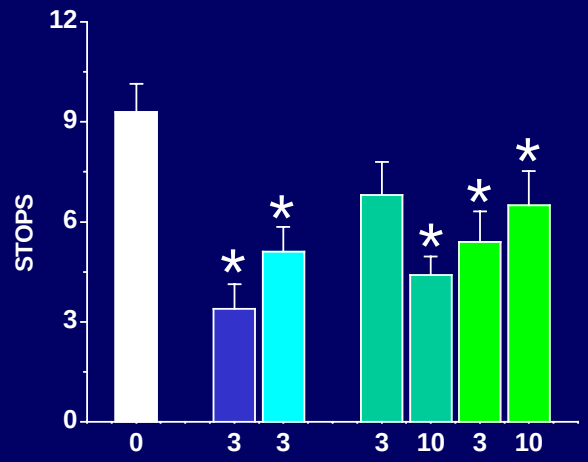
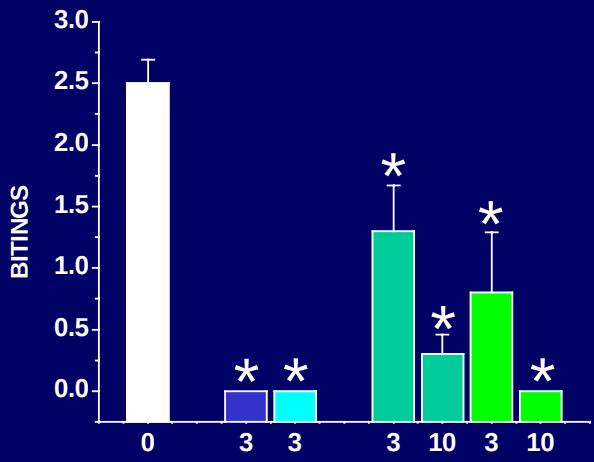
ANXIOLYTIC-LIKE ACTIVITY IN THE MOUSE DEFENSE TEST BATTERY







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

(mg/kg, p.o.)

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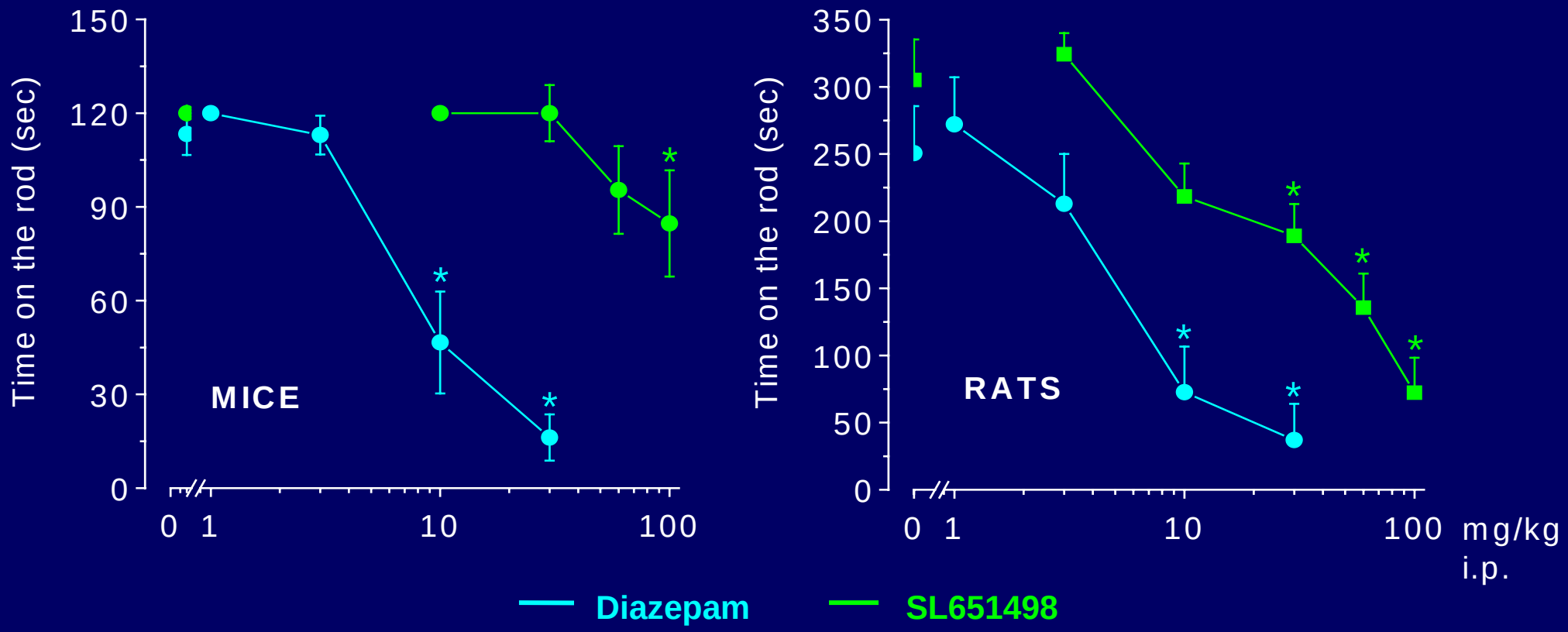
COMPARISON OF THE ANXIOLYTIC-LIKE EFFECTS OF SL651498 WITH THOSE OF OTHER ANXIOLYTICS

	MINIMAL EFFECTIVE DOSE, mg/kg, ip (po)					
	Rat				Mouse	
	Punished Lever	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

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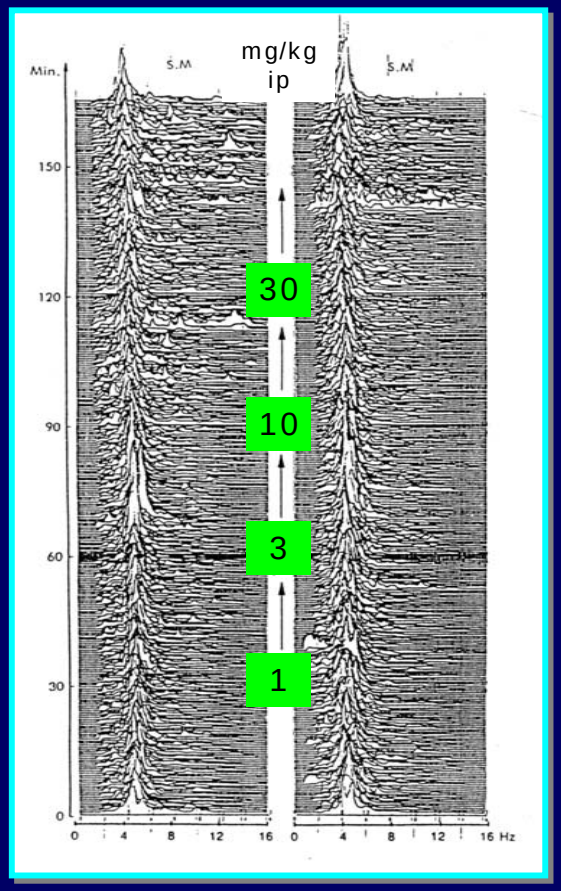
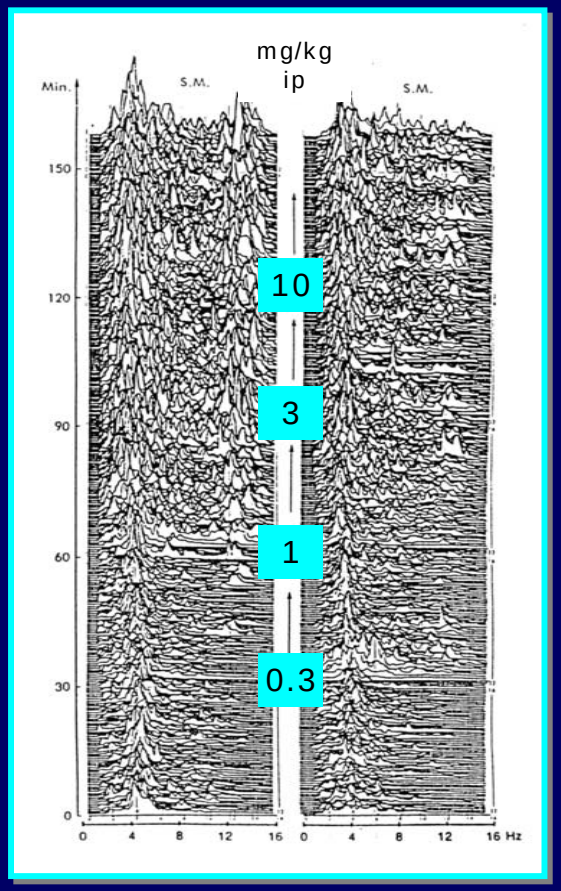
EVALUATION OF THE SEDATIVE PROPERTIES OF SL651498 AS MEASURED BY EEG IN RATS

SL651498



DIAZEPAM



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

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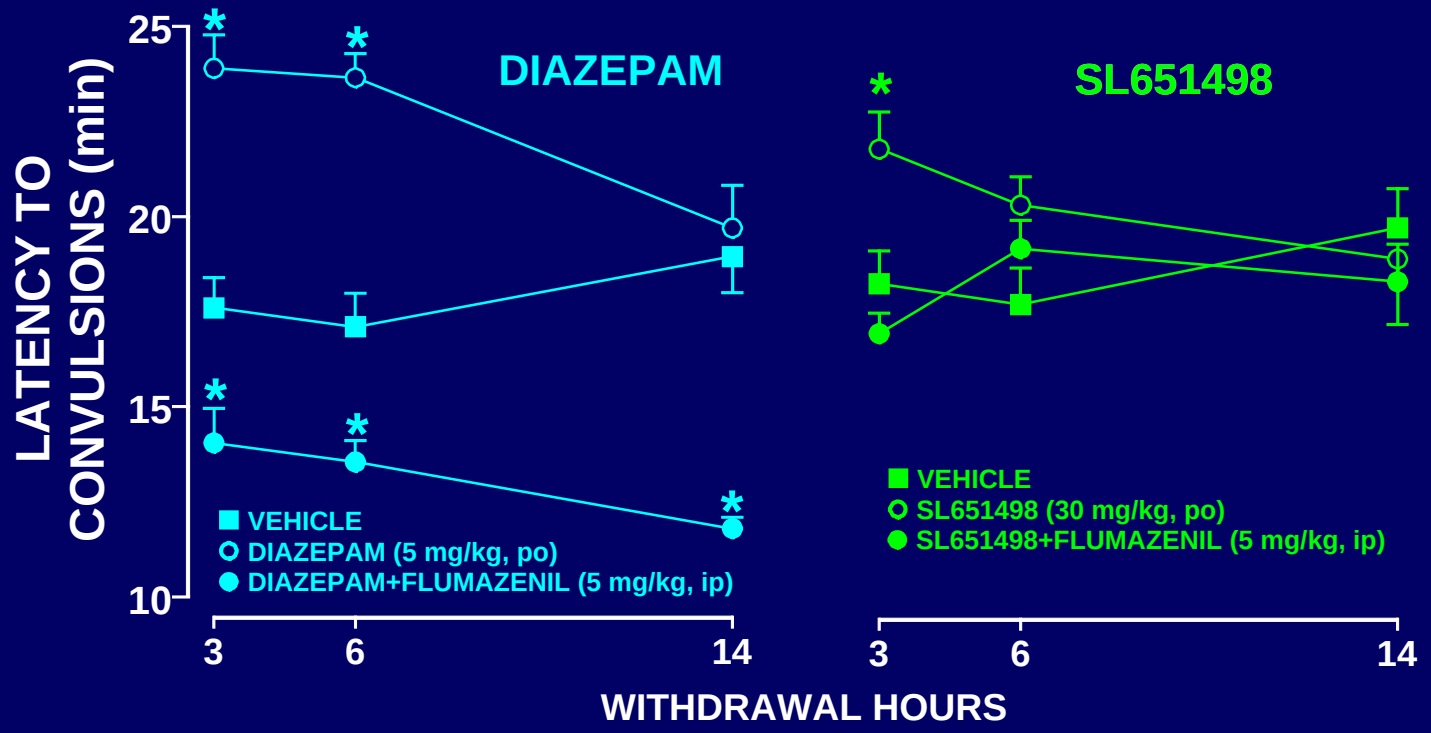
EVALUATION OF THE PROPENSITY TO PRODUCE SIGNS OF WITHDRAWALS FOLLOWING ABRUPT DISCONTINUATION OF REPEATED ADMINISTRATION (10 d/bid) IN THE ISONIAZID-INDUCED CONVULSION TEST IN MICE



SL651498 does not produce signs of withdrawal following abrupt discontinuation

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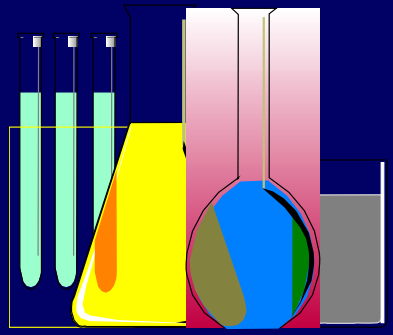
PHARMACOLOGICAL PROPERTIES	EXPECTED CLINICAL PROFILE
High affinity for the $GABA_A$ α_2 subtype	
• Active in classical animal models of anxiety	→ Efficacy in general anxiety disorder
Partial agonist at the $GABA_A$ α_1 subtype	
• No sedation	→ Wide separation between anxiolytic effects and sedation
• Lack of potentiation of the loss of righting reflex induced by ethanol and barbital at anxiolytic doses	→ 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	→ Low propensity to induce cognitive impairment
• Lack of precipitated withdrawal signs after repeated treatment	→ Low liability to induce physical dependence
• Ataxic and myorelaxant effects appear at high doses only	→ Wide separation between anxiolytic and motor effects

SL651498

CHEMISTRY



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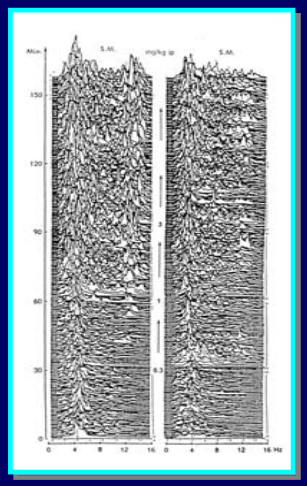

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