CTP-354: A novel deuterated subtype-selective GABA(A) modulator for treatment of neurodevelopmental and anxiety disorders

CTP-354 was developed as a non-benzodiazepine, deuterated analog of L-838417, aiming to improve the metabolic stability of the original GABA(A) receptor agonist. In vitro studies revealed that CTP-354 demonstrated enhanced metabolic stability compared to L-838417, with a PK/PD effect that persisted up to 10 mg/kg doses.

An in vivo study compared CTP-354 and L-838417 for efficacy in models of sedation and ataxia. CTP-354 showed significantly improved metabolic stability and enhanced duration of action compared to L-838417.

CTP-354 was progressed into animal models of sedation/ataxia and neuropathic pain, demonstrating equivalent efficacy to gabapentin in the Chung model with a superior duration of effect.

Conclusions

Deuterium substitution confers metabolic stability:
- CTP-354 exhibited markedly improved metabolic stability relative to L-838417 in vitro in human microsomes from human and rat.
- CTP-354 showed a 3- to 4-fold increase in exposure relative to L-838417 in oral dosing of rat and dog.

Deuterium substitution does not change the intrinsic pharmacology:
- In a selectivity screen with 68 targets, both CTP-354 and L-838417 showed the expected binding to the benzodiazepine site of the GABA(A) receptor with no significant off-target activities.
- CTP-354 retained the in vitro pharmacologic activity of L-838417 in the subtypes tested.

CTP-354 was well tolerated and efficacious in in vivo animal models:
- CTP-354 demonstrated a lack of sedative/adverse effects in the rat model at doses which afforded excellent pain protection in the rat Chung model.
- CTP-354 abolished a PPD effect versus L-838417 in the rat Chung model, with the improved exposure of CTP-354 leading to an enhanced duration of action.
- CTP-354 showed equivalent efficacy to standard-of-care pain drug gabapentin in the rat Chung model with a superior duration of effect.

Literature cited

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