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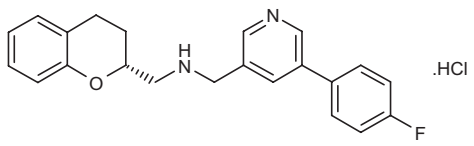
Sarizotan Hydrochloride

Prop INN; USAN

Antidyskinetic Drug
5-HT$_{1A}$ Receptor Agonist
Dopamine D2 Receptor Ligand

EMD-128130
EMR-62225

(–)-(*R*)-*N*-(3,4-Dihydro-2*H*-1-benzofuran-2-ylmethyl)-*N*-[5-(4-fluorophenyl)-3-pyridylmethyl]amine hydrochloride



$C_{22}H_{22}ClFN_2O$
Mol wt: 384.8741

CAS: 195068-07-6

CAS: 351862-32-3 (as free base)

EN: 257398

Abstract

The treatment of Parkinson's disease with levodopa is associated with the development of dyskinesias, or involuntary movements. The risk increases with increasing duration of treatment. Sarizotan exhibits dual 5-HT$_{1A}$ receptor agonism and dopamine D2 receptor ligand activity and is in development for the treatment of dyskinesia associated with Parkinson's disease. In an animal model of Parkinson´s disease, sarizotan reduced levodopa-induced choreiform dyskinesias in monkeys by up to 90% without diminishing the antiparkinsonian efficacy of levodopa. In hemiparkinsonian rats, sarizotan effectively reduced the abnormal involuntary movements, dystonia and contralateral rotations associated with chronic levodopa therapy. In an initial proof-of-concept study in patients with moderate to advanced Parkinson's disease, sarizotan significantly reduced levodopa-induced dyskinesias in a within-patient comparison. The efficacy of sarizotan was further demonstrated in an open-label study in which there was a significant increase between baseline and the final treatment visit in the percent "on" time without dyskinesia. This benefit was maintained in a 1-year follow-up. Sarizotan has been well tolerated in clinical studies to date.

Synthesis

Optical resolution of commercially available racemic 2-(aminomethyl)-3,4-dihydro-2*H*-1-benzopyran (I) through the formation of the diastereomeric salt with *N*-tosyl-L-proline (II), followed by crystallization, yields the (*R*)-enantiomer (III) (1, 2). Alkylation of intermediate (III) can be performed either with 3-(chloromethyl)-5-(4-fluorophenyl)pyridine (IV) in the presence of *N*-methylmorpholine in DMF (1) or alternatively through a reductive alkylation with 5-(4-fluorophenyl)pyridine-3-carbaldehyde (V) and $NaBH_4$ in H_2O/EtOH (2). Scheme 1.

Background

Parkinson's disease is a progressive neurodegenerative disorder characterized by bradykinesia, resting tremor, rigidity and postural instability. The clinical symptoms of Parkinson's disease result from degenerative changes in the substantia nigra and a resulting loss of dopamine-producing cells in the brain. The loss of motor control is mainly attributable to the loss of dopamine content in the nigrostriatal neurons, and the dopaminergic agent levodopa is the mainstay of pharmacological treatment for Parkinson's disease (3, 4). However, treatment with levodopa is associated with the development of dyskinesias, or involuntary movements. Estimates from the literature reveal that the risk of experiencing motor complications and of developing dyskinesias was approximately 40% in patients treated with levodopa therapy for 4-6 years (5), and dyskinesias may impact the quality of life and increase healthcare costs in patients with Parkinson's disease (6).

Sarizotan (EMD-128130, EMR-62225) is a chromane derivative that exhibits dual 5-HT$_{1A}$ receptor agonism and dopamine receptor antagonism/partial agonism (7, 8).

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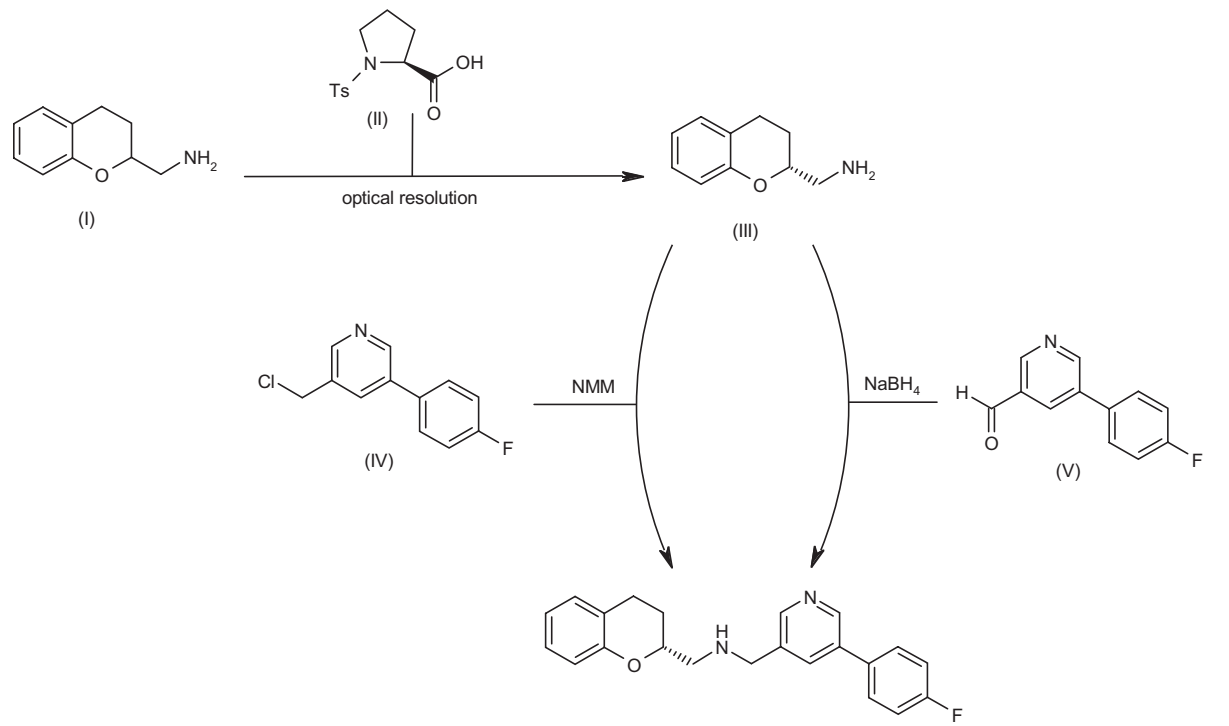
Scheme 1: Synthesis of Sarizotan



The compound was initially developed for the treatment of schizophrenia but is now in phase III clinical trials for the treatment of dyskinesia associated with Parkinson's disease (9).

Preclinical Pharmacology

In vitro, sarizotan demonstrated high binding affinity for human dopamine D2, D3 and D4 receptors and 5-HT_{1A} receptors, with IC_{50} values of < 6 nM. In functional studies in rat striatum, it stimulated dopamine accumulation and inhibited 5-HTP accumulation with respective ED_{50} values of 3 and 1 mg/kg p.o. Sarizotan also inhibited apomorphine-induced climbing in mice (ED_{50} = 5 mg/kg s.c., 20 mg/kg p.o.) and apomorphine-induced stereotyped behavior in rats (ED_{50} = 7 mg/kg s.c., 16 mg/kg p.o.), but no cataleptogenic activity was observed (8).

The receptor pharmacology of sarizotan was further characterized in functional assays in Chinese hamster ovary (CHO) cells stably expressing human 5-HT_{1A} receptors and in AtT-20 mouse pituitary cells expressing human D2S, D3 and D4.4 receptors. Agonist activity was demonstrated at 5-HT_{1A}, D3 and D4.4 receptors, and weak partial agonist activity at D2S receptors. *In vivo*, sarizotan induced hypothermia in rats and mice, demonstrating its activity at both pre- and postsynaptic 5-HT_{1A} receptors. This was reversed by the selective 5-HT_{1A} antagonist WAY-100635 (10, 11). Additional studies in the AtT-20 cell line indicated that sarizotan may induce the D2 receptor to mimic D3 receptor signaling (12). Studies using dual-probe microdialysis in awake rats demonstrated that systemic injection of sarizotan significantly reduced extracellular glutamate levels in the motor cortex and the ipsilateral dorsolateral striatum. The inhibitory effects were counteracted by intracortical infusion of WAY-100135. The findings indicated that the antidyskinetic properties of sarizotan were mediated via its 5-HT_{1A}-agonist actions in the motor cortex, resulting in reduced activity of the corticostriatal glutamate pathways with reduced activation of striatal GABA output neurons in basal ganglia circuitry (11, 13-15).

Evaluation of the neurochemical profile of sarizotan confirmed its receptor profile, with nanomolar affinity for 5-HT_{1A} and D2, D3 and D4 receptors and the profile of a 5-HT_{1A} agonist and dopamine antagonist/partial agonist. In reserpinized rats, at oral doses of 10-30 mg/kg sarizotan decreased DOPA accumulation, and it also induced contralateral rotational behavior in rats with unilateral substantia nigra lesions. These results indicated some intrinsic dopaminergic activity (16).

In rats, sarizotan at doses of 1-10 mg/kg i.p. dose-dependently reduced haloperidol-induced muscle rigidity, which mimics parkinsonian muscle rigidity. It decreased both the mechanical muscle resistance developed in response to passive extension or flexion of the hind foot, and the electromyographic activity of two antagonist muscles. The effect was reversed by WAY-100635. The compound had no effect on normal muscle tone (17).

The response to sarizotan was assessed in animal models of Parkinson's disease. In rats and monkeys rendered parkinsonian, chronic intermittent treatment with levodopa resulted in motor response alterations, as measured by the shortening of the duration of contralateral rotations in rats or dyskinetic movements in monkeys. In 6-OHDA-lesioned rats, sarizotan (2.5 mg/kg p.o.) reduced the shortening in motor response duration induced by chronic levodopa treatment. In MPTP-treated monkeys, a dose of 2 mg/kg p.o. reduced levodopa-induced choreiform dyskinesias by up to 90% without diminishing the antiparkinsonian efficacy of levodopa. The effects of sarizotan were blocked by WAY-100635, indicating that the responses were likely to be related to 5-HT_{1A} receptor stimulation. In these studies, sarizotan had no effect on dyskinesias induced by either a D1 or a D2 agonist (18-20). In a further study in hemiparkinsonian 6-OHDA-lesioned rats, sarizotan (3 mg/kg s.c.) effectively reduced the abnormal involuntary movements, dystonia and contralateral rotations associated with chronic levodopa therapy (21).

In a rat model of tardive dyskinesia, sarizotan dose-dependently reduced repetitive jaw movements induced by a D1 agonist (SKF-38393), with maximal effects achieved at 1.5 mg/kg i.p. Sarizotan also dose-dependently reversed haloperidol-induced repetitive jaw movements when it was administered in the drinking water for 7 weeks during withdrawal from chronic haloperidol treatment. Significant effects were achieved at doses of 1.5 and 9 mg/kg (22-27).

In mice lacking the G-protein regulator RGS9, sarizotan reduced the L-DOPA-elicited truncal dystonia that characteristically develops in these mice (26). The compound also antagonized haloperidol-induced catalepsy in rats (24-27).

Pharmacokinetics and Metabolism

The two main pathways of metabolism of sarizotan are hydroxylation and *N*-dealkylation (28, 29). *In vitro* studies identified cytochrome P-450 CYP1A2 and CYP3A4 as the major isoforms involved in the metabolic conversion of sarizotan (29).

Two single- and two multiple-dose studies were performed in healthy male volunteers to determine the clinical pharmacokinetics of sarizotan. Over the tested dose range of 0.5-25 mg, the area under the curve (AUC) and peak plasma concentrations (C_{max}) increased proportionally to dose; t_{max} ranged from 0.5 to 2.3 h and $t_{1/2}$ from 4.6 to 10.7 h. No accumulation was evident in multiple-dose studies. Sarizotan was well tolerated in healthy volunteers, the most frequently reported adverse events being mild to moderate nausea and headache (30).

Clinical Studies

A PET study in 7 healthy volunteers administered sarizotan at doses up to 50 mg b.i.d. for 5 days revealed significant human D2 receptor occupancy, but no consistent 5-HT_{1A} receptor occupancy (31).

The effects of sarizotan on sleep electroencephalogram and nocturnal hormone secretion were examined in 10 healthy young male volunteers. Sarizotan 20 mg or placebo was administered at 22:00 hours on the examination night according to a randomized schedule in a 2-period crossover study. Sarizotan significantly reduced rapid eye movement (REM) and total sleep time and significantly increased prolactin during the first half of the night (32-34). The results from this and several of the following studies are summarized in Table I.

A double-blind, placebo-controlled, proof-of-concept study was performed in 18 patients with moderate to advanced Parkinson's disease to evaluate the hypothesis that sarizotan would improve dopamine-induced motor complications by reducing striatal serotonergic nerve impulse activity. The patients had received L-DOPA treatment for an average of 6 years and all patients had motor fluctuations and peak-dose dyskinesias. Following a 1-week placebo run-in phase, patients entered a 2-week dose-escalation phase with sarizotan 2 mg twice daily for

Table I: Clinical studies of sarizotan (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind Crossover	Sarizotan, 20 mg p.o. Placebo	10	In healthy male volunteers, sarizotan reduced REM sleep while increasing prolactin and adrenocorticotropin hormone levels in the first half of the night	32, 34
Parkinson's disease	Randomized Double-blind	Placebo x 1 wk → Sarizotan, 2 mg b.i.d. p.o. x 1 wk → Sarizotan, 5 mg b.i.d. p.o. x 1 wk	18	Sarizotan was well tolerated and more effective than placebo in reducing the severity of levodopa-induced dyskinesia in patients with advanced Parkinson's disease. Sarizotan induced no antiparkinsonian effects and did not modify the antiparkinsonian response of an optimal levodopa dose	35-37
Parkinson's disease	Open Multicenter	Sarizotan, 2 mg b.i.d. x 1 wk → 5 mg b.i.d. x 1 wk → 10 mg b.i.d. x 10 wks	64	Sarizotan significantly reduced dyskinesia, especially troublesome dyskinesia, in levodopa-treated Parkinson's disease patients	38

1 week, increasing to 5 mg twice daily in the second week. Motor function was assessed at the end of each period for analysis of primary (dyskinesias) and secondary (parkinsonism and wearing off) efficacy parameters for within-patient comparisons. Sarizotan alone or with optimal- or low-dose levodopa had no effect on parkinsonian severity. At a dose of 5 mg twice daily, it significantly reduced levodopa-induced dyskinesias by 40% compared with levodopa alone, without significantly decreasing the antiparkinsonian response of the optimal levodopa dose. Sarizotan was well tolerated, with the majority of adverse events being considered unrelated to the study drug (35-37).

The safety and efficacy of sarizotan in Parkinson's disease patients with dyskinesia were further evaluated in an open-label, multicenter, dose-escalation study (the SPLENDID study). A total of 64 patients with advanced Parkinson's disease and dyskinesias entered the study, which consisted of a 3-week titration phase, a 9-week maintenance phase and a 2-week withdrawal phase. Sarizotan was initiated at a dose of 2 mg twice daily, increasing to 5 mg and to a maximum of 10 mg twice daily during week 3. The dose remained constant during the maintenance phase. The primary efficacy variable was the change between baseline and final treatment visit in the percent "on" time without dyskinesia, as measured in the patients' diaries. There was a significant increase in this parameter, from a mean of 3.7 h at baseline to 6.0 h at the end of the maintenance phase, representing an increase from 23% to 38% of the waking day. There were also significant benefits with sarizotan treatment on secondary efficacy parameters. The mean total daily dose of sarizotan at the final treatment visit was 8.9 mg, with the most common dose received by patients being 2 mg twice daily. Sarizotan was well tolerated and most adverse events were related to aggravated parkinsonism, which were resolved by an adaptation to or reduction of the sarizotan dose. There were no significant laboratory abnormalities (38).

Patients who participated in the SPLENDID study could continue on open-label sarizotan for up to 24 months. Doses were individually titrated over a 6-week period to the optimal doses of 2, 5, 7 or 10 mg twice daily established in the SPLENDID study. Forty-six patients entered the follow-up study. In a 1-year interim analysis, the time spent "on" without dyskinesia (the primary efficacy variable) increased by 1.4-2.4 h/day compared to baseline. This represented an increase from 24% to 39% of the waking day. The duration and severity of dyskinesia were significantly reduced at all visits compared with baseline. The most frequent adverse event was worsening of Parkinson's disease in 63% of patients. Aggravated dyskinesia occurred in 20% of patients. Fourteen of 36 serious adverse events reported were considered possibly related to sarizotan (39, 40).

Drug Interactions

A randomized, double-blind study was performed in 18 healthy volunteers to evaluate the risk of interactions with drugs cleared by cytochrome P-450 enzymes. Sarizotan had no effect on the pharmacokinetic profiles of metoprolol (CYP2D6), caffeine (CYP1A2), mephenytoin (CYP2C19), diclofenac (CYP2C9) or midazolam (CYP3A4), as demonstrated by bioequivalence criteria (41, 42).

Double-blind, randomized, crossover studies were also performed in healthy male volunteers to investigate the effects of sarizotan on the pharmacokinetics of digoxin (n=12) and levodopa (n=16). In the digoxin study, subjects received digoxin 0.25 mg/day with either sarizotan 2 mg twice daily or placebo. Treatment was given for 10 days, then the alternative treatment was given following a 19-day washout phase. Steady-state digoxin pharmacokinetics did not change significantly following co-administration of sarizotan (43). In the levodopa study, subjects received levodopa 100 mg 3 times daily and either carbidopa or benserazide for 5 days, with or without sarizotan 5 mg twice daily. Sarizotan had no statistically or clinically relevant effects on the pharmacokinetics of levodopa (44).

Source

Merck KGaA (DE).

References

1. Böttcher, H., Devant, R., Greiner, H., Bartoszyk, G., Berthelon, J.-J., Noblet, M., Zeiller, J.-J., Brunet, M. (Merck Patent GmbH). *Amino(thio)ether derivatives as CNS active agents*. CA 2160447, EP 0707007, EP 1123933, JP 1996225501, US 5767132.

2. Bokel, H.-H., Neunfeld, S., Gantzert, L., Knierieme, R., Simon, E., Devant, R., Helm, U., Reubold, H. (Merck Patent GmbH). *Method for producing 2[-5-(4-fluorophenyl)-3-pyridylmethyl-aminomethyl]-chromane*. CA 2445207, DE 10120619, EP 1383763, US 2004138266, WO 2002088117.

3. Prous Science Drug R&D Backgrounders: *Parkinson's Disease*. Updated March 23, 2006.

4. Fahn, S. *Description of Parkinson's disease as a clinical syndrome*. Ann NY Acad Sci 2003, 991: 1-14.

5. Ahlskog, J.E., Muenter, M.D. *Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature*. Mov Disord 2001, 16(3): 448-58.

6. Péchevis, M., Clarke, C.E., Vierregge, P., Khoshnood, B., Deschaseaux-Voinet, C., Berdeaux, G., Ziegler, M. *Effects of dyskinesias in Parkinson's disease on quality of life and health-related costs: A prospective European study*. Eur J Neurol 2005, 12(12): 956-63.

7. Böttcher, H., Bartoszyk, G.D., Berthelon, J.J., Brunet, M., Devant, R., Greiner, H.E., Gottschlich, R., März, J., Seyfried, C.A., Zeiller, J.J. *SAR for novel chromanes: Atypical neuroleptics with 5HT1A agonistic and D2 antagonistic activity*. Soc Neurosci Abst 1996, 22(Part 2): Abst 334.1.

8. Bartoszyk, G.D., Greiner, H.E., Seyfried, C.A. *Pharmacological profile of EMD 128130: A putative atypical antipsychotic with dopamine D2 antagonistic and serotonin 5-HT1A agonistic properties*. Soc Neurosci Abst 1997, 23(Part 1): Abst 207.5.

9. *Sarizotan HCl in patients with Parkinson's disease suffering from treatment-associated dyskinesia (NCT00105521)*. ClinicalTrials.gov Web Site 2006, January 4.

10. Bartoszyk, G.D., Kuzhikandathil, E.V. *Receptor pharmacology of the antidyskinetic drug sarizotan*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst PT039-11.

11. Kuzhikandathil, E.V., Bartoszyk, G.D., Antonelli, T., Tomasini, M.C., Fuxe, K., Tanganelli, S. *Receptor pharmacology of the antidyskinetic drug sarizotan*. Mov Disord 2006, 21(Suppl. 13): Abst P66.

12. Kuzhikandathil, E.V., Sayed, N., Pasuit, J.B., Bartoszyk, G.D. *Differential effects of sarizotan on dopamine receptor function*. 34th Annu Meet Soc Neurosci (Oct 23-27, San Diego) 2004, Abst 163.6.

13. Antonelli, T., Fuxe, K., Tomasini, M.C., Bartoszyk, G.D., Seyfried, C.A., Tanganelli, S., Ferraro, L. *Effects of sarizotan on the corticostriatal glutamate pathways*. Synapse 2005, 58(3): 193-9.

14. Antonelli, T., Fuxe, K., Tomasini, M.C., Bartoszyk, G.D., Tanganelli, S., Ferraro, L.N. *Effects of the antidyskinetic drug sarizotan on corticostriatal glutamate pathways*. 130th Annu Meet Am Neurol Assoc (ANA) (Sept 25-28, San Diego) 2005, Abst 66.

15. Fuxe, K., Antonelli, T., Tomasini, M.C., Bartoszyk, G.D., Tanganelli, S., Ferraro, L. *Effects of sarizotan on the corticostriatal glutamate pathways*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst PT022-02.

16. Bartoszyk, G.D., van Amsterdam, C., Greiner, H.E., Rautenberg, W., Russ, H., Seyfried, C.A. *Sarizotan, a serotonin 5-HT1A receptor agonist and dopamine receptor ligand. 1. Neurochemical profile*. J Neural Transm - Gen Sect 2004, 111(2): 113-26.

17. Lorenc-Koci, E., Wardas, J., Bartoszyk, G.D., Wolfarth, S. *Contribution of the serotonin 5-HT1A receptor agonism of 8-OH-DPAT and EMD 128130 to the regulation of haloperidol-induced muscle rigidity in rats*. Neuropharmacology 2003, 45(8): 1057-69.

18. Bibbiani, F., Oh, J.D., Chase, T.N. *Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models*. Neurology 2001, 57(10): 1829-34.

19. Bibbiani, F., Oh, J.D., Chase, T.N. *Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models*. 54th Annu Meet Am Acad Neurol (AAN) (April 13-20, Denver) 2002, Abst P05.092.

20. Bibbiani, F., Oh, J.D., Chase, T.N. *Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models*. Soc Neurosci Abst 2001, 27: Abst 292.3.

21. Schmidt, W.J. *Sarizotan counteracts L-DOPA-induced dyskinesia syndrome in parkinsonian rats*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst PT022-03.

22. Rosengarten, H., Bartoszyk, G.D., Quartermain, D., Lin, Y. *The effect of chronic administration of sarizotan, 5-HT1A agonist/D3/D4 ligand, on haloperidol-induced repetitive jaw movements in rat model of tardive dyskinesia*. Prog Neuro-Psychopharmacol Biol Psychiatry 2006, 30(3): 273-9.

23. Rosengarten, H., Bartoszyk, G.D., Kretschmer, B.D. *Mechanism of antidyskinetic action of sarizotan in tardive dyskinesias*. 130th Annu Meet Am Neurol Assoc (ANA) (Sept 25-28, San Diego) 2005, Abst 65b.

24. Bartoszyk, G.D., Rosengarten, H., Schmidt, W.J. *Antidyskinetic efficacy of sarizotan in animal models of Parkinson's disease and tardive dyskinesia*. 130th Annu Meet Am Neurol Assoc (ANA) (Sept 25-28, San Diego) 2005, Abst 65a.

25. Bartoszyk, G.D., Rosengarten, H. *Efficacy of sarizotan in animal models of tardive dyskinesia*. 16th Int Congr Parkinson's Dis Relat Disord (June 5-9, Berlin) 2005, Abst PT022-01.

26. Gerlach, M., Bartoszyk, G.D., van den Buuse, M., Schwarz, J., Riederer, P. *Antidyskinetic efficacy of sarizotan*. Mov Disord 2006, 21(Suppl. 13): Abst P67.

27. Bartoszyk, G.D., Schmidt, W.J. *Mechanism of antidyskinetic action of sarizotan*. Mov Disord 2006, 21(Suppl. 13): Abst P65.

28. Hewitt, N.J., Bühring, K.-U., Dasenbrock, J., Haunschild, J., Ladstetter, B., Utesch, D. *Studies comparing in vivo:in vitro metabolism of three pharmaceutical compounds in rat, dog, monkey, and human using cryopreserved hepatocytes, microsomes, and collagen gel immobilized hepatocyte cultures*. Drug Metab Dispos 2001, 29(7): 1042-50.

29. Haunschild, J., Thiel, I., Dasenbrock, J. *Identification of the cytochrome P450 isoforms involved in the metabolism of EMD 128 130*. Exp Toxic Pathol 1998, 50(2): 107.

30. Tillner, J., Krosser, S., Fluck, M., Ungethum, W., Kovar, A. *Sarizotan: A review of its clinical pharmacokinetics*. Mov Disord 2006, 21(Suppl. 13): Abst P234.

31. Rabiner, E.A., Gunn, R.N., Wilkins, M.R., Sedman, E., Grasby, P.M. *Evaluation of EMD 128 130 occupancy of the 5-HT1A and the D2 receptor: A human PET study with [11C]WAY-100635 and [11C]raclopride*. J Psychopharmacol 2002, 16(3): 195-9.

32. Kuenzel, H.E., Steiger, A., Held, K., Antonijevic, I.A., Frieboes, R.-M., Murck, H. *Changes in sleep electroencephalogram and nocturnal hormone secretion after administration of the antidyskinetic agent sarizotan in healthy young male volunteers*. Psychopharmacology (Berlin) 2005, 180(2): 327-32.

33. Held, K., Frieboes, R.M., Murck, H., Künzel, H., Ziegenbein, M., Steiger, A. *Effects of an atypical neuroleptic EMD 128130 on sleep EEG and nocturnal hormone secretion in young normal controls*. Eur Neuropsychopharmacol 2000, 10(Suppl. 3): Abst P.2.120.

34. Held, K., Frieboes, R.M., Murck, H., Künzel, H., Ziegenbein, M., Steiger, A. *Effects of a putative atypical neuroleptic sarizotan on sleep EEG and nocturnal hormone secretion in male healthy volunteers*. Int J Neuropsychopharmacol 2000, 3(Suppl. 1): Abst P.01.018.

35. Bara-Jimenez, W., Bibbiani, F., Morris, M.J., Dimitrova, T., Sherzai, A., Mouradian, M.M., Chase, T.N. *Effects of serotonin 5-HT1A agonist in advanced Parkinson's disease*. Mov Disord 2005, 20(8): 932-6.

36. Bara-Jimenez, W., Sherzai, A., Bibbiani, F., Gillespie, M., Morris, M.J., Mouradian, M.M., Chase, T.N. *5-HT1A agonist effects in advanced Parkinson's disease*. Neurology 2003, 60(5, Suppl. 1): Abst S59.003.

37. Adwan, Z.S. *5-HT1A agonist effect in advanced Parkinson's disease*. 7th Int Conf Prog Alzheimer Parkinson Dis (March 9-13, Sorrento) 2005, Abst.

38. Olanow, C.W., Damier, P., Goetz, C.G., Mueller, T., Nutt, J., Rascol, O., Serbanescu, A., Deckers, F., Russ, H. *Multicenter, open-label, trial of sarizotan in Parkinson disease patients with levodopa-induced dykinesias (the SPLENDID study)*. Clin Neuropharmacol 2004, 27(2): 58-62.

39. Olanow, C.W. *Sarizotan has long-term efficacy in reducing levodopa-induced dykinesia in patients with Pakrinson's disease*. Mov Disord 2006, 21(Suppl. 13): Abst P238.

40. Olanow, C.W. *Sarizotan is well tolerated during long-term treatment of levodopa-induced dyskinesia in patients with Parkinson's disease*. Mov Disord 2006, 21(Suppl. 13): Abst P237.

41. Krosser, S., Neugebauer, R., Dolgos, H., Kovar, A. *Effect of sarizotan on the pharmacokinetics of probe drugs for major cytochrome P450 isoenzymes: A combined cocktail study*. Mov Disord 2006, 21(Suppl. 13): Abst P232.

42. Krösser, S., Neugebauer, R., Dolgos, H., Kovar, A. *Effect of sarizotan on a cocktail of cytochrome P 450 substrates*. 33rd Annu Meet Am Coll Clin Pharmacol (ACCP) (Oct 3-5, Phoenix) 2004, Abst 50.

43. Tillner, J., Krosser, S., Fluck, M., Kovar, A. *Sarizotan does not influence the pharmacokinetics or safety of digoxin in healthy male volunteers*. Mov Disord 2006, 21(Suppl. 13): Abst P231.

44. Krosser, S., Tillner, J., Kovar, A. *Sarizotan does not change levodopa pharmacokinetics*. Mov Disord 2006, 21(Suppl. 13): Abst P233.

Additional References

Bruins Slot, L.A., Newman-Tancredi, A., Cussac, D. *Effects of novel antipsychotic agents at dopamine D2 and serotonin 5-HT12A receptors: Measure of mitogen-activated protein kinase phosphorylation*. 35th Annu Meet Soc Neurosci (Nov 12-16, Washington DC) 2005, Abst 373.7.

Bardin, L., Kleven, M.S., Grevoz-Barret, C., Newman-Tancredi, A. *Antipsychotic-like versus cataleptogenic actions in mice of novel antipsychotics having D2 antagonist and 5-HT1A agonist properties*. 35th Annu Meet Soc Neurosci (Nov 12-16, Washington DC) 2005, Abst 913.4.

Cosi, C., Assie, M.B., Leduc, N., Ormiere, A.M., Newman-Tancredi, A. *In vitro affinity and efficacy of novel antipsychotics having mixed D2 antagonist/5-HT1A agonist properties*. 33rd Annu Meet Soc Neurosci (Nov 8-12, New Orleans) 2003, Abst 956.3.

Newman-Tancredi, A., Assie, M.-B., Leduc, N., Ormiere, A.-M., Danty, N., Cosi, C. *Novel antipsychotics activate recombinant human and native rat serotonin 5-HT1A receptors: Affinity, efficacy and potential implications for treatment of schizophrenia*. Intl J Neuropsychopharmacol 2005, 8(3): 341-56.

Assie, M.-B., Ravailhe, V., Faucillon, V., Newman-Tancredi, A. *Contrast in contribution of 5-hydroxytryptamine 1A receptor activation to neurochemical profile of novel antipsychotics: Frontocortical dopamine and hippocampal serotonin release in rat brain*. J Pharmacol Exp Ther 2005, 315(1): 265-72.

Assie, M., Consul-Denjean, N., Archimbeaud, V., Faucillon, V., Dominguez, H., Newman-Tancredi, A. *In vivo affinity of various antipsychotic compounds for dopamine D2-like receptors in mouse striatum*. 35th Annu Meet Soc Neurosci (Nov 12-16, Washington DC) 2005, Abst 913.3.

Assie, M., Ravailhe, V., Faucillon, V., Maraval, M., Carilla-Durand, E., Newman-Tancredi, A. *Novel antipsychotics having mixed D2 antagonist/5-HT1A agonist properties. Effects on cerebral monoamines and plasma prolactin*. 33rd Annu Meet Soc Neurosci (Nov 8-12, New Orleans) 2003, Abst 956.1.

Kleven, M.S., Prinssen, E.P.M., Koek, W., Grevoz-Barret, C., Newman-Tancredi, A. *In vivo pharmacology of novel antipsychotics having mixed D2 antagonist/5HT1A agonist properties: Evidence for lowered EPS liability*. 33rd Annu Meet Soc Neurosci (Nov 8-12, New Orleans) 2003, Abst 956.2.

Kleven, M.S., Barret-Grevoz, C., Brunis Slot, L., Newman-Tancredi, A. *Novel antipsychotic agents with 5-HT1A agonist properties: Role of 5-HT1A receptor activation in attenuation of catalepsy induction in rats*. Neuropharmacology 2005, 49(2): 135-43.

Kanthasamy, A.G., Ranade, S., Sun, F., Bartoszyk, G., Kanthasamy, A. *Antimyoclonic and neuroprotective effects of sarizotan in an animal model of cardiac arrest-induced posthypoxic myoclonus*. 35th Annu Meet Soc Neurosci (Nov 12-16, Washington DC) 2005, Abst 470.6.