COL-144: PRECLINICAL PROFILE OF A SELECTIVE 5-HT$_{1F}$ RECEPTOR AGONIST FOR MIGRAINE

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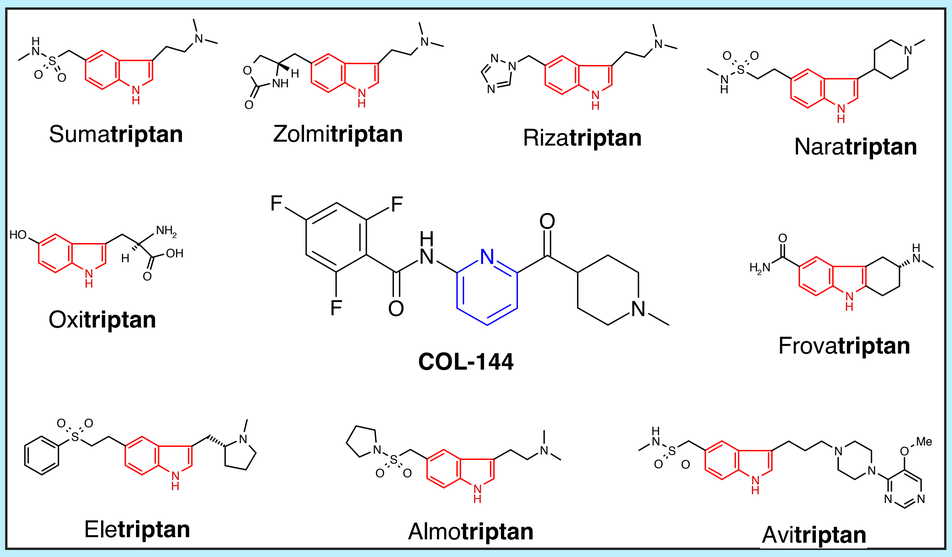
Introduction

Neurally acting anti-migraine agents (NAAMAs) represent a paradigm shift in migraine therapy through their non-vasoconstrictor mechanism of action (Goadsby, Nature Rev. Drug Disc. 2005; 4:751). A leading approach in this class is selective 5-HT$_{1F}$ receptor agonists. Proof of concept for this mechanism was obtained in several clinical studies using the prototypical compound LY334370 (Goldstein et al., Lancet 2001; 358:1230).

COL-144 (CoLucidPharmaceuticals Inc.; formerly LY573144), is a new generation **5-HT$_{1F}$** receptor agonist with greater selectivity and improved drugability compared to LY334370.

COL-144 has a novel chemical structure, distinct from triptans



Methods

The methods are summarized in the following publications:

Radioligandand [35S]GTPγS binding:
- Wainscottet al., Eur. J. Pharmacol. 1998; 352:117.
- Wainscottet al., NaunynSchmiedebergsArch. Pharmacol. 2005; 371:169.

Vasoconstriction assay:
- Cohen and Schenck. Br. J. Pharmacol. 2000; 131:562.

Preclinical models of migraine:
- Fillaet al., J Med Chem. 2002, 45(20):4383-6.
- Johnson et al., Neuroreport. 1997, 8(9-10):2237-40.

Receptor Selectivity

COL-144 has high affinity for the 5-HT$_{1F}$ receptor and is highly selective relative to other 5-HT receptor subtypes.

Binding Affinity of COL-144 at Human 5-HT Receptor Subtypes[a]

Ki (nM)									
5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{1e}$	**5-HT$_{1F}$**	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	5-HT$_{6}$	5-HT$_{7}$
1053 ± 134 (8)	1043 ± 124 (8)	1357 ± 156 (8)	594 ± 59.1 (6)	**2.21 ± 0.22 (8)**	>5 μM (6)	>2 μM (6)	>3 μM (6)	>4 μM (6)	>3 μM

[a]values expressed as K_i in nM (unless otherwise indicated) are means ± SEM of the number of experiments shown in parentheses.
> indicates that less than 50% inhibition was obtained at the specified concentration.

COL-144 was also evaluated by NovaScreen (Hanover, MD) for selectivity across >50 GPCRs and ion channels. At 1μM it produced <50% inhibition of radiolignd binding at all sites examined, except for 67% inhibition at the benzodiazepine binding site.

COL-144 showed high potency and selectivity in an assay of 5-HT$_{1F}$ receptor agonist efficacy in vitro.

Stimulation of [^{35}S]GTPγS Binding by Activation of Human Cloned 5-HT Receptor Subtypes

Receptor	EC$_{50}$ (nM)	Emax (%)	% Stimulation at 10μM	N
5-HT$_{1A}$	ND	ND	15.7 ± 1.4	(12)
5-HT$_{1B}$	ND	ND	49.0 ± 2.2	(7)
5-HT$_{1D}$	ND	ND	73.2 ± 4.6	(7)
5-HT$_{1e}$	ND	ND	54.6 ± 2.5	(7)
5-HT$_{1F}$	43.1 ± 2.6	80.9 ± 1.4		(15)

EC$_{50}$ = concentration of compound producing 50% of maximal response
Emax = Maximal response expressed as a percent of the response produced by 10 μM 5-HT
ND = EC$_{50}$ could not be determined because of low potency at the receptor
N = number of experiments

Functional Selectivity

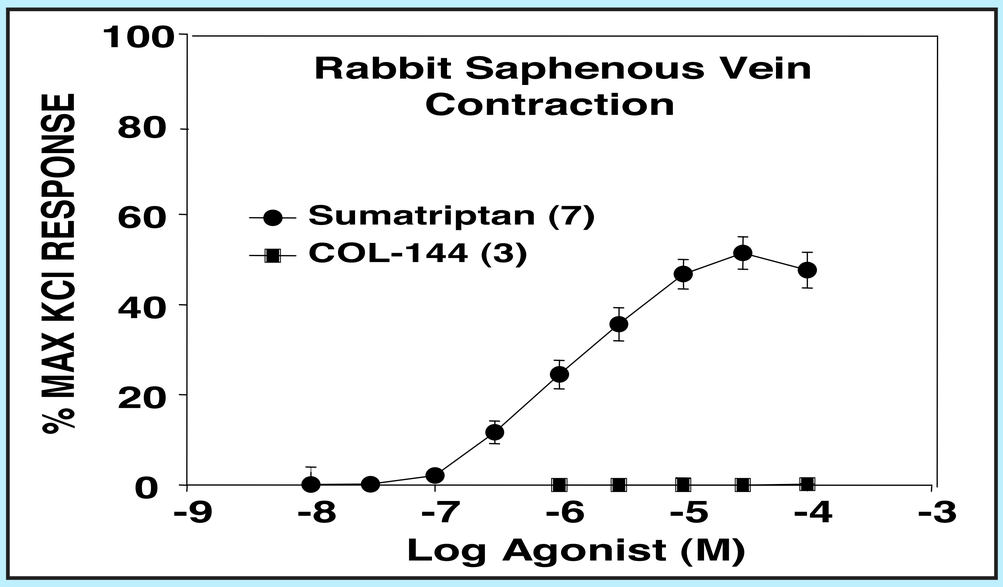
COL-144, unlike triptans, has functional selectivity for 5-HT$_{1F}$ receptors relative to 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors.

EC$_{50}$ values (nM) for In Vitro Activation of Cloned Human Receptors*

Drug	5HT$_{1A}$	5HT$_{1B}$	5HT$_{1D}$	5HT$_{1e}$	5HT$_{1F}$
Sumatriptan	>10,000	70	3	~10,000	247
Zolmitriptan	~10,000	20	1	62	417
Rizatriptan	>10,000	119	5	870	2540
Naratriptan	~10,000	7	2	31	19
Frovatriptan	1,150	20	2	>10,000	367
COL-144	>10,000	~10,000	>1,000	~10,000	43

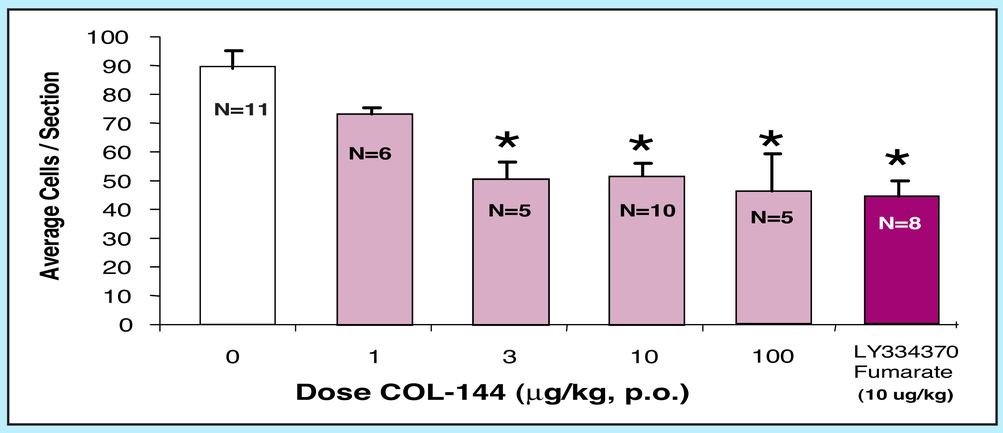
*Measured as the stimulation of [^{35}S]GTPγS binding. Each value is the mean of 4-15 separate determinations

COL-144 produced no contraction of the rabbit saphenous vein, compared to a 50% contraction by sumatriptan.

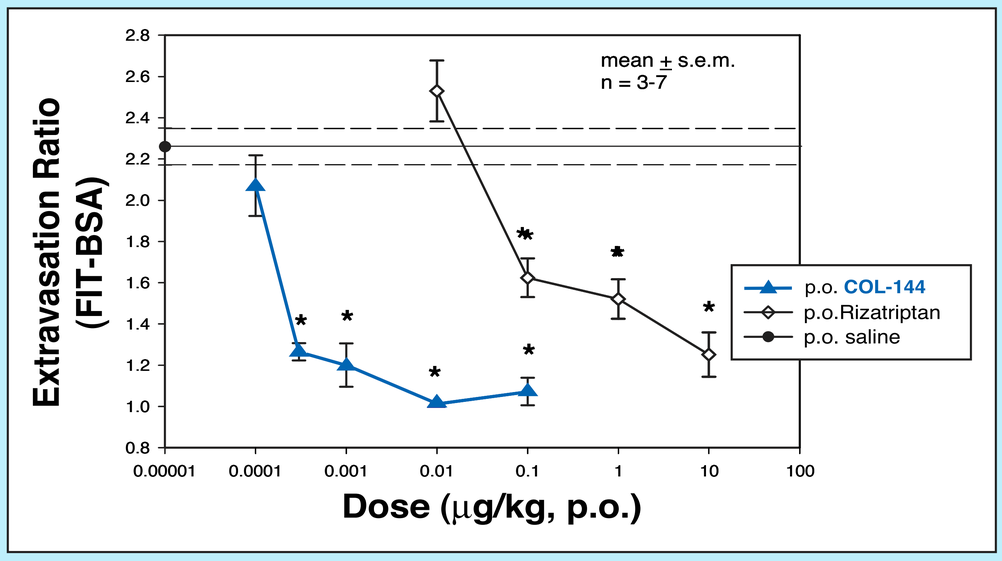


In Vivo Activity

COL-144 inhibited trigeminal stimulation-induced c-fos expression in the nucleus caudalis of rats 1 hour after oral dosing.



COL-144 inhibited dural plasma protein extravasation produced by trigeminal stimulation in rats 1 hour after oral dosing.



Rizatriptan is included for comparison. Statistical analysis was performed by comparison to saline control group using Student's t-test (*p<0.05).

Conclusions

- **COL-144** is a high affinity, potent, and selective agonist at the 5-HT$_{1F}$ receptor.
  o >450-fold higher affinity for 5-HT$_{1F}$ versus 5-HT$_{1B}$ or $_{1D}$ receptors.
- **COL-144** has functional selectivity for the 5-HT$_{1F}$ receptor relative to other sub types, including 5-HT$_{1B/1D}$.
- Unlike triptans, **COL-144** is not a vasoconstrictor.
- **COL-144** inhibits the effects of trigeminal ganglion stimulation in preclinical models of migraine.
- **COL-144** has the potential to treat migraine without vasoconstriction.