Supplementary material

Supplementary Table 1. Reference tracers (concentration, nM), and reference competitors used for radioligand binding competition assays for the different receptors studied. *Historical pIC_{50} values obtained at Ogeda S.A. (now Epics Therapeutics S.A., Gosselies, Belgium). Values represent mean values ± SEM of a stated number of averaged technical duplicates (n).

Receptor	Reference tracer	Assay concentration (nM)	Reference competitor	Historical* pIC_{50} (reference competitor)	Estimated pIC_{50} (reference competitor)	pK_i (reference competitor)
5-HT_{1A}	[^{3}H]-8-OH-DPAT	0.39	5-HT hydrochloride	8.83 ± 0.04 (23)	9.00 ± 0.06 (2)	9.51 ± 0.06 (2)
5-HT_{1B}	[^{3}H]-5-CT	0.60	5-HT hydrochloride	8.42 ± 0.10 (8)	8.61 ± 0.19 (2)	9.09 ± 0.19 (2)
5-HT_{1D}	[^{3}H]-5-CT	0.50	5-HT hydrochloride	8.35 ± 0.08 (7)	8.67 ± 0.18 (2)	9.35 ± 0.18 (2)
5-ht_{1E}	[^{3}H]-LSD	14.0	BRL-54443	8.49 ± 0.09 (5)	8.44 ± 0.07 (3)	8.74 ± 0.07 (3)
5-HT_{1F}	[^{3}H]-LSD	8.00	BRL-54443	8.59 ± 0.17 (5)	8.54 ± 0.12 (3)	8.96 ± 0.12 (3)
5-HT_{2A}	[^{3}H]-Ketanserin	1.48	Ketanserin	8.22 ± 0.18 (6)	8.17 ± 0.04 (2)	8.69 ± 0.04 (2)
5-HT_{2B}	[^{3}H]-Mesulergin	1.00	5-HT hydrochloride	7.67 ± 0.09 (8)	7.68 ± 0.05 (3)	7.89 ± 0.05 (3)
5-HT_7	[^{3}H]-LSD	1.00	5-CT maleate	9.28 ± 0.05 (13)	9.42 ± 0.17 (3)	9.51 ± 0.17 (3)

Supplementary Table 2. Reference agonists for second messenger activation assays of cAMP (5-$HT_{1A/B/E/F}$ and 5-HT_7), GTPγS (5-HT_{1D}) and IP (5-$HT_{2A/B}$). *Historical pEC_{50} values obtained at Ogeda S.A. (now Epics Therapeutics S.A., Gosselies, Belgium). Values represent mean values ± SEM of a stated number of averaged technical duplicates (n).

Receptor	Reference agonist	Historical* pEC_{50} cAMP/IP/ GTPγS	Estimated pEC_{50} cAMP/IP/ GTPγS
5-HT_{1A}	5-CT maleate	9.18 ± 0.05 (35)	9.02 ± 0.17 (4)
5-HT_{1B}	5-CT maleate	8.78 ± 0.07 (23)	8.80 ± 0.01 (2)
5-HT_{1D}	5-CT maleate	9.30 ± 0.05 (21)	9.26 ± 0.13 (3)
5-ht_{1E}	5-HT hydrochloride	9.00 ± 0.16 (2)	8.61 ± 0.05 (3)
5-HT_{1F}	5-HT hydrochloride	8.94 ± 0.15 (7)	8.69 ± 0.16 (3)
5-HT_{2A}	α-Me-5-HT	8.68 ± 0.05 (31)	8.33 ± 0.06 (2)
5-HT_{2B}	α-Me-5-HT	9.70 ± 0.09 (28)	9.63 ± 0.08 (2)
5-HT_7	5-CT maleate	9.59 ± 0.03 (45)	9.62 ± 0.01 (3)

Supplementary Table 3. Summary of pEC_{50} values of vasoconstriction of the human coronary artery. These values represent the negative logarithm of the molar concentration of these compounds at which 50% of their maximal response was exerted. When a compound was devoid of vasoconstrictor activity, a pEC_{50} of 5 was set.

Agonist	pEC_{50}	Reference
5-HT hydrochloride	6.50	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998; Parsons et al., 1998)
5-CT maleate	6.44	(MaassenVanDenBrink, Reekers, Bax & Saxena, 2000)
Ergotamine tartrate	7.81	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998)
Sumatriptan succinate	6.11	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998)
Zolmitriptan	6.33	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998)
Naratriptan hydrochloride	6.78	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998)
Rizatriptan benzoate	6.36	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998)
Eletriptan hydrobromide	5.54	(van den Broek et al., 2000)
Frovatriptan Racemate	7.86	(Parsons et al., 1998)
Donitriptan hydrochloride	8.25	(van den Broek et al., 2002)
Avitriptan fumarate	7.06	(MaassenVanDenBrink, Reekers, Bax, Ferrari & Saxena, 1998; Saxena et al., 1997)
Lasmiditan hemisuccinate	5.00	

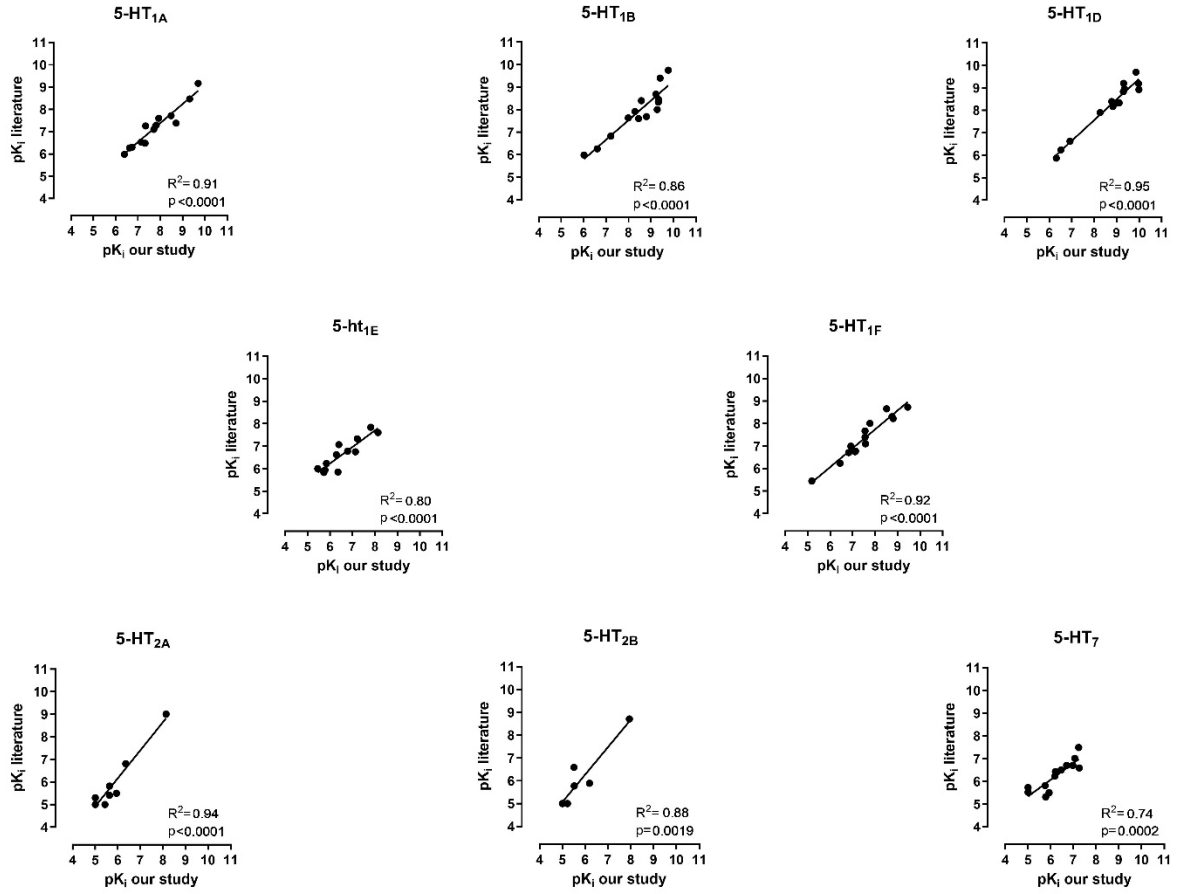
Supplementary Table 4. Comparison pIC_{50} (negative logarithm of the molar concentration of these compounds at which 50% of the radioligand is displaced) and pK_i (negative logarithm of the molar concentration of the dissociation constant) values of individual antimigraine drugs at 5-$HT_{1A/B/D/E/F,}$ 5-$HT_{2A/B}$ and 5-HT_7 receptors obtained in our study and values reported in the literature (Lit.) obtained from Adham et al., 1993a; Adham et al., 1993b; Bard, Kucharewicz, Zgombick, Weinshank, Branchek & Cohen, 1996; Barf et al., 1996; Beer, Heald, McAllister & Stanton, 1998; Bhalla, Sharma, Ma, Wurch, Pauwels & Saxena, 2001; Bou et al., 2000; Brüss, Kiel, Bönisch, Kostanian & Göthert, 2005; Castro et al., 1997; Choi et al., 2008; Comer & Hons, 2002; Connor et al., 1997; Deleu & Hanssens, 2000; Dickenson & Hill, 1998; Dupuis, Perez, Halazy, Colpaert & Pauwels, 1999; Ghoneim, Ibrahim, El-Deeb, Lee & Booth, 2011; Glennon et al., 2000; Goadsby, 1998; Gras, Llenas, Jansat, Jáuregui, Cabarrocas & Palacios, 2002; Hoyer, 1988; John et al., 1999; Johnson et al., 1997; Knight et al., 2004; Leonhardt, Herrick-Davis & Titeler, 1989; Leysen et al., 1996; Lovenberg et al., 1993; Martin et al., 1997; McAllister et al., 1992; Napier, Stewart, Melrose, Hopkins, McHarg & Wallis, 1999; Nelson et al., 2010; Newman-Tancredi et al., 1997; Pauwels, Palmier, Dupuis & Colpaert, 1998; Pauwels, Palmier, Wurch & Colpaert, 1996; Pauwels, Tardif, Palmier, Wurch & Colpaert, 1997; Phebus et al., 1997; Razzaque et al., 1999; Schmuck, Ullmer, Kalkman, Probst & Lübbert, 1996; Shen, Monsma, Metcalf, Jose, Hamblin & Sibley, 1993; Stanton & Beer, 1997; Sternfeld et al., 1999; Street et al., 1995; Vries, Villalón & Saxena, 1999; Wang et al., 2013; Wurch, Palmier & Pauwels, 2000; Xu et al., 1999; Zgombick, Schechter, Macchi, Hartig, Branchek & Weinshank, 1992; Zgombick, Weinshank, Macchi, Schechter, Branchek & Hartig, 1991; Zhang et al., 2004.

Agonist	5-HT_{1A}				5-HT_{1B}				5-HT_{1D}				5-ht_{1E}				5-HT_{1F}				5-HT_{2A}				5-HT_{2B}				5-HT_7			
	pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i		pIC_{50}		pK_i	
	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.
Ergotamine tartrate	9.19	9.11	9.70	9.17	8.87	-	9.34	8.45	8.63	-	9.31	9.20	6.08	-	6.39	7.07	6.71	-	7.13	6.78	7.62	8.19	8.14	9.01	7.73	8.46	7.94	8.71	7.13	7.49	7.23	7.49
Sumatriptan succinate	6.63	6.32	7.14	6.53	7.81	8.12	8.29	7.92	8.31	7.98	9.00	8.32	5.42	5.40	5.72	5.83	7.13	7.70	7.55	7.67	<5	<5	<5	<5	<5	<5	<5	<5	6.10	5.44	6.19	6.23
Zolmitriptan	7.28	6.50	7.79	7.26	8.85	8.21	9.33	8.33	9.28	8.75	9.97	9.19	7.51	-	7.81	7.84	7.13	7.27	7.55	7.39	<5	<5	<5	<5	<5	<5	<5	-	6.97	-	7.06	7.01
Naratriptan hydrochloride	7.31	6.90	7.82	7.29	8.75	-	9.22	8.69	8.62	-	9.30	8.83	7.83	-	8.13	7.61	8.33	-	8.75	8.31	<5	-	<5	<5	<5	-	5.08	-	5.84	-	5.93	5.5
Rizatriptan benzoate	6.81	6.50	7.32	6.48	7.51	7.39	7.99	7.63	8.15	7.63	8.83	8.17	6.48	-	6.78	6.78	6.40	-	6.82	6.71	<5	5.20	<5	<5	5.30	-	5.51	6.59	<5	-	<5	5.73
Almotriptan malate	6.23	6.07	6.73	6.30	7.97	7.92	8.45	7.60	7.57	7.89	8.26	7.90	<5	-	<5	-	7.15	7.30	7.57	7.10	<5	<5	<5	<5	<5	<5	<5	<5	6.36	5.50	6.46	6.5
Eletriptan hydrobromide	8.20	-	8.71	7.38	8.80	-	9.28	8.00	9.31	-	9.99	8.92	6.91	-	7.21	7.33	7.35	-	7.77	8.01	5.42	-	5.94	<5.5	6.14	-	6.35	-	6.61	-	6.70	6.7
Frovatriptan racemate	6.83	-	7.34	7.26	8.09	-	8.57	8.40	8.10	-	8.78	8.39	<5	-	5.18	-	6.50	-	6.92	7.00	<5	-	<5	5.30	<5	-	<5	-	6.88	-	6.97	6.70
Donitriptan hydrochloride	7.42	-	7.93	7.60	9.29	-	9.77	9.75	9.18	-	9.86	9.70	5.47	-	5.77	5.94	<5	-	5.18	5.45	5.83	-	6.35	6.81	5.88	-	6.09	-	6.12	-	6.21	6.43
Avitriptan fumarate	7.20	-	7.71	7.10	8.32	-	8.80	7.69	8.42	-	9.11	8.33	5.15	-	5.45	6.00	6.69	-	7.11	6.75	5.11	-	5.63	-	5.73	-	5.94	-	6.03	-	6.12	-
Alniditan dihydrochloride	8.81	8.32	9.32	8.47	8.93	9.03	9.41	9.40	8.66	8.65	9.35	8.96	5.98	6.2	6.28	6.62	6.02	6.2	6.44	6.24	<5	<5	5.43	<5	6.67	-	6.88	-	7.16	6.5	7.26	6.59
Lasmiditan hemisuccinate	5.88	-	6.39	5.98	5.54	-	6.02	5.98	5.62	-	6.31	5.87	5.54	-	5.84	6.23	8.09	-	8.51	8.66	<5	-	<5	<5	5.01	-	5.22	<5	<5	-	<5	<5
LY334370 hydrochloride	7.98	-	8.49	7.72	6.74	-	7.21	6.82	6.24	-	6.92	6.62	6.83	-	7.13	6.75	9.03	-	9.45	8.73	5.11	-	5.63	5.82	5.98	-	6.19	5.89	5.66	-	5.75	5.81
LY344864 hydrochloride	6.12	-	6.63	6.27	6.13	-	6.61	6.26	5.83	-	6.52	6.24	6.05	-	6.35	5.85	8.38	-	8.80	8.22	5.11	-	5.63	5.41	5.31	-	5.52	5.77	5.69	-	5.78	5.31

Supplementary Table 5. Comparison of pEC_{50} values of cAMP (5-$HT_{1A/B/E/F}$ and 5-HT_7), GTPγS (5-$HT_{1A/B/D/E/F}$) and IP (5-HT_2) assays of individual antimigraine drugs obtained in our study and the historical values reported in the literature (Lit.). These values represent the negative logarithm of the molar concentration of these compounds at which 50% of their maximal response is exerted. The lesser than 5 symbol (<5) indicates that less than 50% response was obtained at 10 µM. Historical values were obtained from Beer, Heald, McAllister & Stanton, 1998; Bhalla, Sharma, Ma, Wurch, Pauwels & Saxena, 2001; Bou et al., 2000; Castro et al., 1997; Dupuis, Perez, Halazy, Colpaert & Pauwels, 1999; John et al., 1999; Johnson et al., 1997; Nelson et al., 2010; Newman-Tancredi et al., 1997; Pauwels, Palmier, Dupuis & Colpaert, 1998; Pauwels, Tardif, Palmier, Wurch & Colpaert, 1997; Razzaque et al., 1999; Schmuck, Ullmer, Kalkman, Probst & Lübbert, 1996; Stanton & Beer, 1997; Sternfeld et al., 1999; Wang et al., 2013 and Xu et al., 1999.

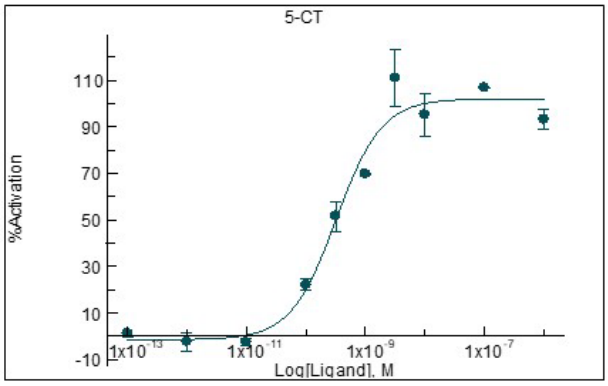
Agonist	5-HT_{1A}				5-HT_{1B}				5-HT_{1D}		5-ht_{1E}				5-HT_{1F}				5-HT_{2A}		5-HT_{2B}		5-HT_7	
	pEC_{50} cAMP		pEC_{50} GTP		pEC_{50} cAMP		pEC_{50} GTP		pEC_{50} GTP		pEC_{50} cAMP		pEC_{50} GTP		pEC_{50} cAMP		pEC_{50} GTP		pEC_{50} IP		pEC_{50} IP		pEC_{50} cAMP	
	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.	Our	Lit.
Ergotamine tartrate	9.78	-	9.63	-	9.94	9.58	9.52	-	9.43	-	5.95	-	5.74	-	5.97	-	6.30	-	9.25	-	8.72	-	7.09	-
Sumatriptan succinate	<5	<5	<5	5.34	7.32	7.73	7.91	6.87	8.30	7.76	5.99	-	5.79	5.00	8.03	7.46	6.80	6.61	<5	<5	<5	5.18	5.22	<5
Zolmitriptan	<5	-	5.52	5.65	7.87	7.89	8.42	7.43	9.51	8.91	8.18	-	7.81	7.21	8.00	8.15	6.67	6.38	<5	<5	<5	<5	6.28	5.30
Naratriptan hydrochloride	<5	-	6.52	5.78	8.05	7.805	8.86	7.81	8.80	8.46	7.75	-	8.17	7.50	8.38	8.66	8.05	7.71	<5	-	<5	-	<5	-
Rizatriptan benzoate	<5	-	<5	5.44	7.08	7.34	7.56	6.63	8.11	7.89	7.34	-	6.90	-	6.54	7.60	5.91	-	<5	-	5.49	5.65	<5	-
Almotriptan malate	<5	-	5.48	-	7.08	8.80	7.85	-	7.75	-	<5	-	<5	-	7.79	-	6.90	-	<5	5	5.20	<5	<5	-
Eletriptan hydrobromide	5.74	-	6.38	-	8.00	8.44	8.09	-	9.04	-	7.53	-	6.90	-	8.13	-	6.88	-	6.07	6.12	6.81	-	6.45	-
Frovatriptan racemate	<5	-	6.12	5.94	7.98	-	8.14	7.70	8.36	8.64	5.04	-	<5	<5	7.10	-	6.35	6.44	<5	-	<5	-	7.42	-
Donitriptan hydrochloride	5.94	-	6.74	-	9.96	9.51	9.52	8.74	9.51	9.08	<5	-	<5	-	<5	-	<5	-	8.10	-	7.61	6.74	5.23	-
Avitriptan fumarate	<5	-	6.19	-	8.57	-	8.68	-	9.27	-	5.52	-	<5	-	7.09	-	6.05	-	6.91	-	6.41	-	5.38	-
Alniditan dihydrochloride	7.00	-	7.29	6.94	8.87	-	8.90	-	8.20	-	5.68	-	5.21	-	5.92	-	5.17	-	<5	-	7.15	-	6.32	-
Lasmiditan hemisuccinate	<5	-	<5	<5	<5	-	<5	<5	6.64	<5	6.17	-	5.34	<5	8.43	-	7.80	7.37	<5	-	<5	-	<5	-
LY334370 hydrochloride	5.84	-	6.96	-	6.52	-	5.80	-	6.92	-	7.53	-	6.95	-	9.08	8.82	9.38	-	<5	-	<5	-	<5	-
LY344864 hydrochloride	<5	-	<5	-	<5	-	5.82	-	6.93	-	6.22	-	6.12	-	8.72	-	7.85	-	<5	-	<5	-	<5	<5

Supplementary Figure 1. Correlation between the pK_i values obtained from literature and the pK_i values obtained in our study for lasmiditan, triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, donitriptan, avitriptan) and other 5-HT receptors ligands (ergotamine, alniditan, 5-HT, 5-carboxamidotryptamine). For references see Supplementary Table 5.

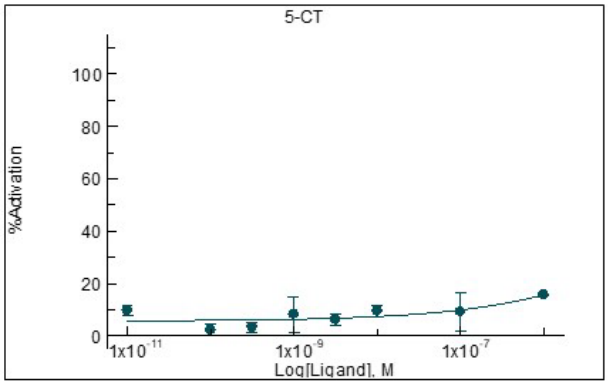


Supplementary Figure 2. Functional responses (cAMP assay) to 5-CT in CHO cells transfected with 5-HT_{1B} receptor (upper) and in CHO cells transfected with an unrelated G protein-coupled receptor.

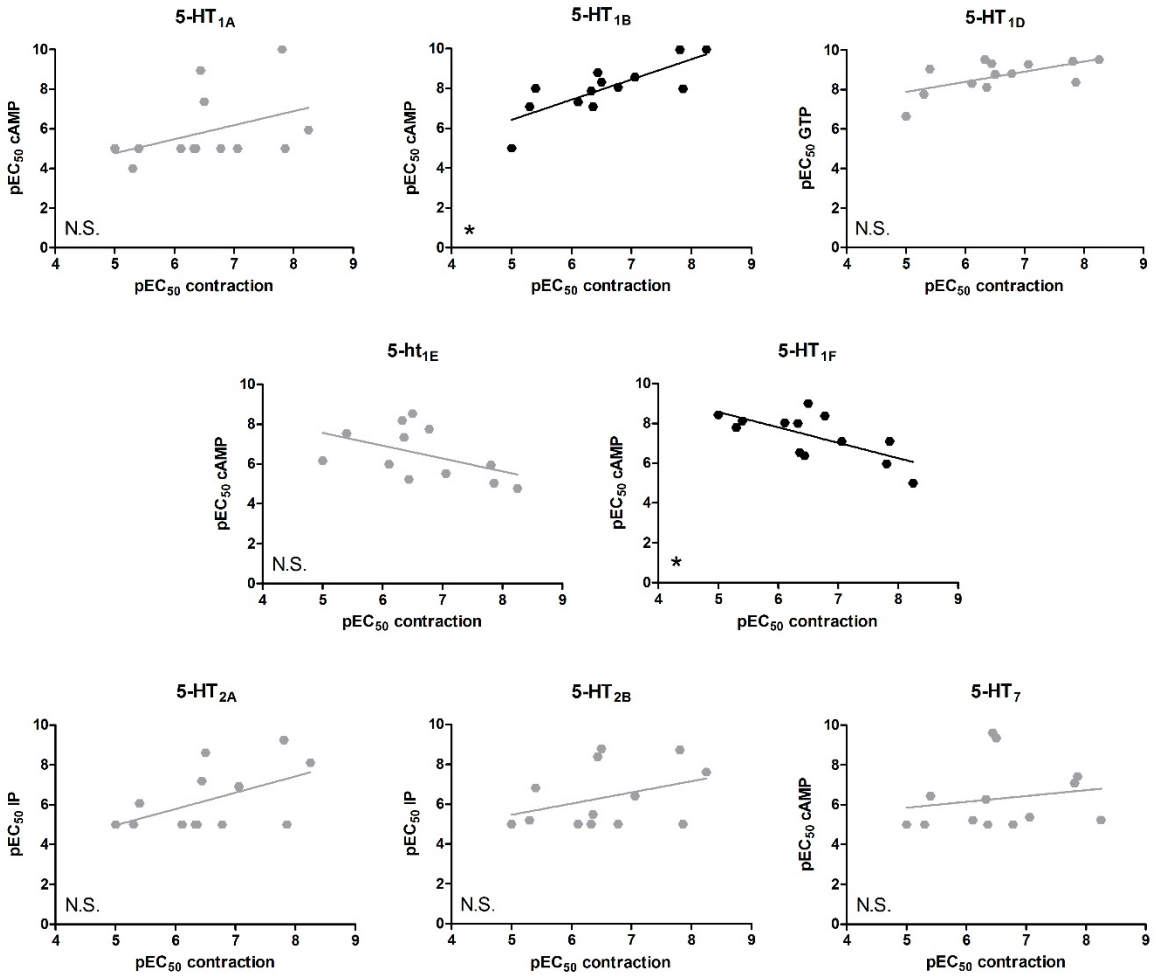
5-HT_{1B} receptor transfected CHO cells



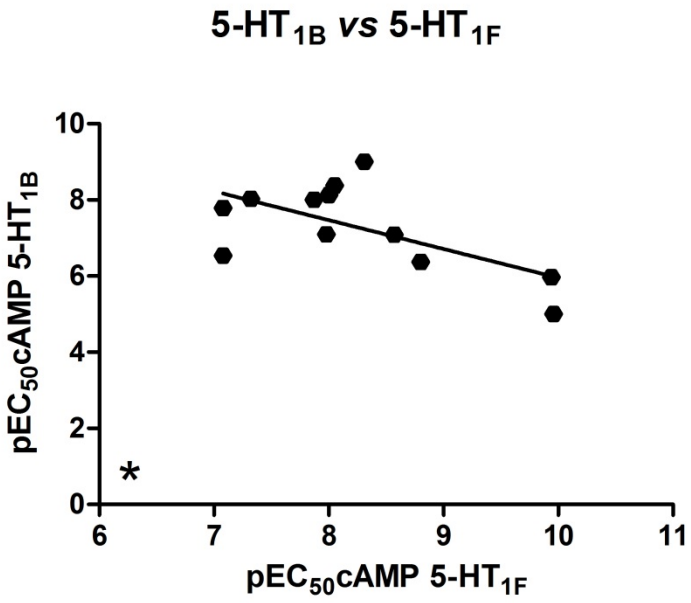
Non-5-HT_{1B} receptor transfected CHO cells



Supplementary Figure 3. Correlation between second messenger activation (*i.e.* cAMP, IP) and the contractile potency of lasmiditan, triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, donitriptan, avitriptan) and other 5-HT receptors ligands (ergotamine, 5-HT, 5-CT) in human isolated coronary arteries; N.S., non-significant; *P<0.05.



Supplementary Figure 4. Correlation between the second messenger activation of 5-HT_{1B} receptor *vs* 5-HT_{1F} receptor by lasmiditan, triptans (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, donitriptan, avitriptan) and other 5-HT receptors ligands (ergotamine, 5-HT, 5-carboxamidotryptamine) in human isolated coronary arteries; $^{*}P<0.05$.



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