

PYRROLOPYRIMIDINE DERIVATIVES AS NR2B NMDA RECEPTOR ANTAGONISTS

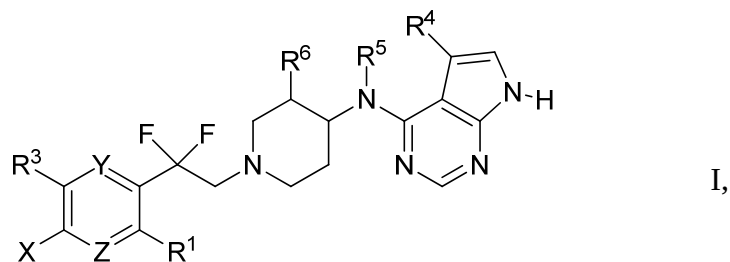
BACKGROUND

[001] Non-selective NMDA receptor antagonists, originally developed in stroke and head trauma, have more recently shown clinical efficacy in treating depression. The non-selective NMDA receptor antagonist, ketamine, has been shown to have rapid onset and efficacy in depression resistant to standard monoamine reuptake inhibitor therapy (Mathews and Zarate, 2013, *J. Clin. Psychiatry* 74:516-158). However, non-selective NMDA receptor antagonists such as ketamine have a range of undesirable pharmacological activities which limit application in humans. In particular dissociative or psychogenic side effects are particularly prominent for non-selective NMDA receptor antagonists. More recently, NR2B subtype selective NMDA receptor antagonists have demonstrated potential in a wide range of clinical indications. In particular, NR2B antagonists have also demonstrated antidepressant activity in early stage clinical trials (Ibrahim et al., 2012, *J. Clin. Psychopharmacol.* 32, 551-557; Preskorn et al., 2008, *J. Clin. Psychopharmacol.* 28, 631-637). Furthermore, selective NR2B antagonists have advantages over unselective NMDA receptor antagonists such as ketamine due to greatly diminished dissociative side effects. However, NR2B antagonists described to date have generally exhibited drawbacks with regard to other drug properties which have limited potential use in human drug therapy.

SUMMARY

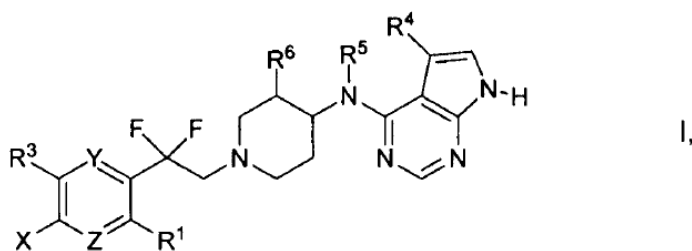
[002] For broad scope of application and safe human use in a range of clinical indications including depression, improved NR2B subtype selective antagonists are needed. The present disclosure, among other things, addresses the need for NR2B receptor antagonists that are improved in one or more aspects exemplified by pharmacokinetic performance, oral activity, cardiovascular safety, and *in vitro* and *in vivo* therapeutic safety index measures.

[003] In some embodiments, the present disclosure encompasses the insight that chemical entities of formula I:



wherein X, Y, Z, R¹, R³, R⁴, R⁵ and R⁶ are defined herein, are NR2B subtype selective receptor antagonists. Chemical entities of formula I, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases and disorders associated with NR2B receptor antagonism. Such diseases and disorders include those described herein.

In one aspect of the present disclosure, there is provided a chemical entity, which is a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Y and Z are independently N or C(R²);

X is -H; halo; C₁-C₆ alkyl optionally substituted with 1 to 6 fluoro; C₃-C₆ cycloalkyl; C₁-C₄ alkoxy optionally substituted with 1 to 6 fluoro; -CN; -NO₂; -N(R⁷)(R⁸); -SR⁷; -S(O)₂R⁹; or -C(O)OR⁷;

R¹ is -H; halo; C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro; C₃-C₆ cycloalkyl; C₁-C₄ alkoxy optionally substituted with 1 to 3 fluoro; -CN; -NO₂; -N(R⁷)(R⁸); -C(O)OR⁷; or -C(O)N(R⁷)(R⁸);

R² is -H; halo; C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro; cyclopropyl; or C₁-C₄ alkoxy optionally substituted with 1 to 3 fluoro;

R³ is -H, -F, -Cl, -CH₃, -CF₃ or -OCH₃;

R⁴ is -H; -F; -Cl; C₁-C₃ alkyl optionally substituted with 1 to 3 fluoro; or cyclopropyl;

R⁵ is -H or -CH₃;

R⁶ is -H, -F or -CH₃;

each instance of R⁷ independently is C₁-C₄ alkyl;

each instance of R⁸ independently is -H or C₁-C₄ alkyl; and

R⁹ is C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the chemical entity disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect of the present disclosure, there is provided a chemical entity disclosed herein for use in treating a disease or disorder responsive to NR2B

In another aspect of the present disclosure, there is provided a use of the chemical entity disclosed herein in the manufacture of a medicament for treating a disease or disorder responsive to NR2B.

BRIEF DESCRIPTION OF THE DRAWING

[004] FIG. 1 shows the results of compound C-178 in the forced swim test as described in Example 2.4.1.

[005] FIG. 2 shows the results of compound C-179 in the forced swim test as described in Example 2.4.2.

[006] FIG. 3 shows the results of compound C-6 in the haloperidol-induced catalepsy model as described in Example 2.5.1.

[007] FIG. 4 shows the results of compound C-12 in the haloperidol-induced catalepsy model as described in Example 2.5.2.

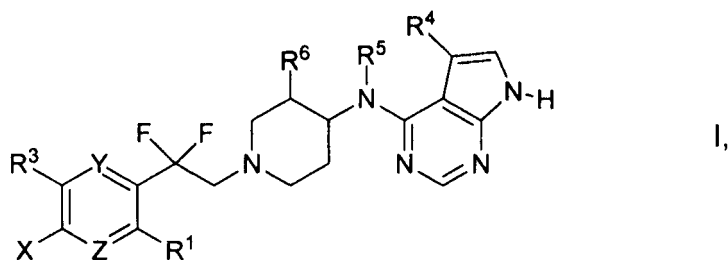
[008] FIG. 5 shows the results of compound C-5 in the haloperidol-induced catalepsy model as described in Example 2.5.3.

[009] FIG. 6 shows the results of compound C-11 in the electroconvulsive threshold test as described in Example 2.6.1.

[010] FIG. 7 shows the results of compound C-127 in the electroconvulsive threshold test as described in Example 2.6.2.

Claims

1. A chemical entity, which is a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

Y and Z are independently N or C(R²);

X is -H; halo; C₁-C₆ alkyl optionally substituted with 1 to 6 fluoro; C₃-C₆ cycloalkyl; C₁-C₄ alkoxy optionally substituted with 1 to 6 fluoro; -CN; -NO₂; -N(R⁷)(R⁸); -SR⁷; -S(O)₂R⁹; or -C(O)OR⁷;

R¹ is -H; halo; C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro; C₃-C₆ cycloalkyl; C₁-C₄ alkoxy optionally substituted with 1 to 3 fluoro; -CN; -NO₂; -N(R⁷)(R⁸); -C(O)OR⁷; or -C(O)N(R⁷)(R⁸);

R² is -H; halo; C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro; cyclopropyl; or C₁-C₄ alkoxy optionally substituted with 1 to 3 fluoro;

R³ is -H, -F, -Cl, -CH₃, -CF₃ or -OCH₃;

R⁴ is -H, -F, -Cl; C₁-C₃ alkyl optionally substituted with 1 to 3 fluoro; or cyclopropyl;

R⁵ is -H or -CH₃;

R⁶ is -H, -F or -CH₃;

each instance of R⁷ independently is C₁-C₄ alkyl;

each instance of R⁸ independently is -H or C₁-C₄ alkyl; and

R⁹ is C₁-C₄ alkyl optionally substituted with 1 to 3 fluoro.

2. The chemical entity of claim 1, wherein:

X is -H, -F, -Cl, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CH₂CF₂CF₃, -CH(CF₃)₂, cyclopropyl, -OCH₃, -OCF₃, -OCHF₂, -OCFH₂, -CN, -NO₂, -NH(CH₃), -N(CH₃)₂, -N(CH₃)(CH₂CH₃), -SCH₃, -SCH₂CH₃, -SO₂CH₃, -SO₂CH₂CH₃ or -SO₂CF₃;

R¹ is -H, -F, -Cl, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, cyclopropyl, -OCH₃, -OCF₃, -OCHF₂, -OCFH₂, -CN, -NO₂, -CO₂CH₃, -CO₂CH₂CH₃, -C(O)N(CH₃)₂, -C(O)NH(CH₃) or -C(O)N(CH₃)(CH₂CH₃);

R² is -H, -F, -Cl, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, cyclopropyl, -OCH₃, -OCF₃, -OCHF₂ or -OCFH₂;

R³ is -H, -F, -Cl, -CH₃, -CF₃ or -OCH₃;

R⁴ is -H, -F, -Cl, -CH₃ or cyclopropyl;

R⁵ is -H or -CH₃; and

R⁶ is -H, -F or -CH₃.

3. The chemical entity of claim 1, wherein:

X is -H, -F, -Cl, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, -CHF₂, -CH₂F, cyclopropyl, -OCH₃, -OCF₃, -OCHF₂, -CN or -SCH₃;

R¹ is -H, -F, -Cl, -CH₃ or -CF₃;

R² is -H, -F, -Cl, -CH₃ or -CF₃;

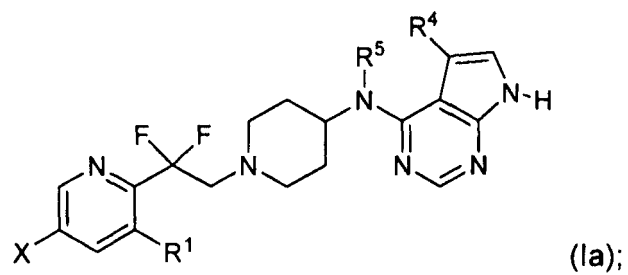
R³ is -H, -F, -Cl, -CH₃ or -CF₃;

R⁴ is -H, -Cl or -CH₃;

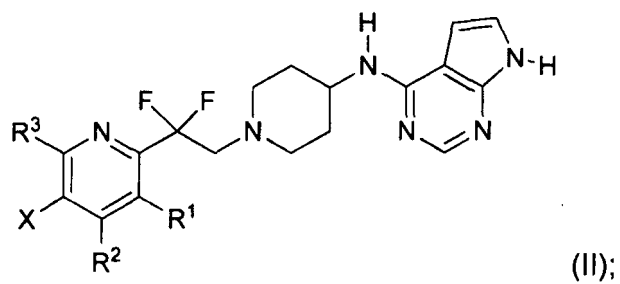
R⁵ is -H or -CH₃; and

R⁶ is -H, -F or -CH₃.

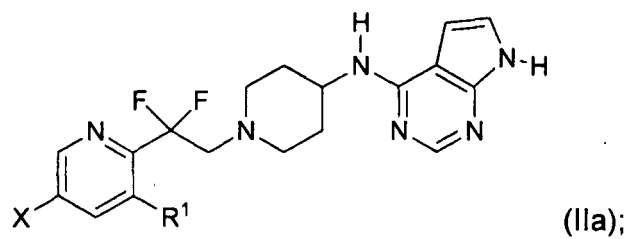
4. The chemical entity of any of claims 1-3, which is a chemical entity of formula (Ia):



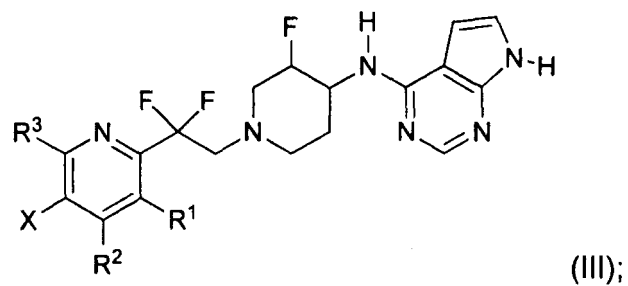
or:
which is a chemical entity of formula (II):



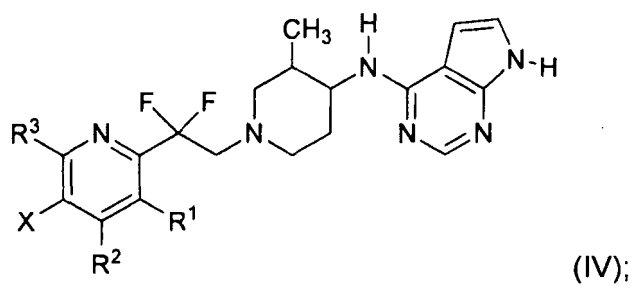
or:
which is a chemical entity of formula (IIa):



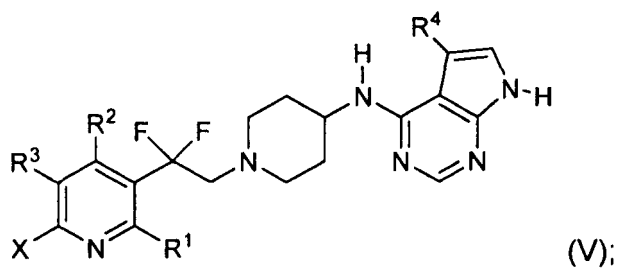
or:
which is a chemical entity of formula (III):



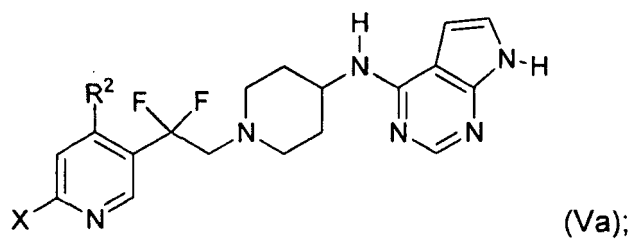
or:
which is a chemical entity of formula (IV):



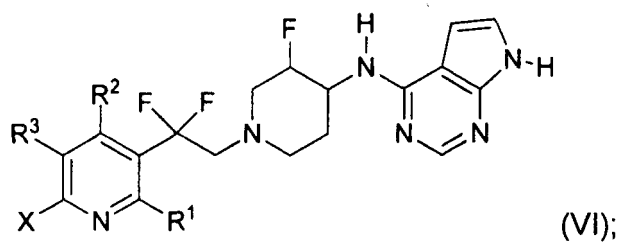
or:
which is a chemical entity of formula (V):



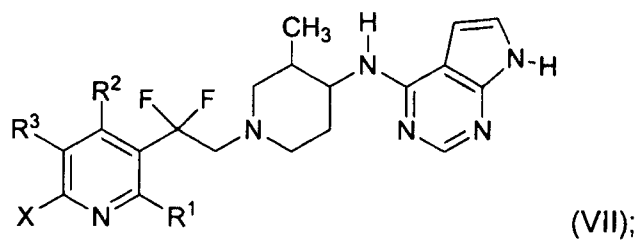
or:
which is a chemical entity of formula (Va):



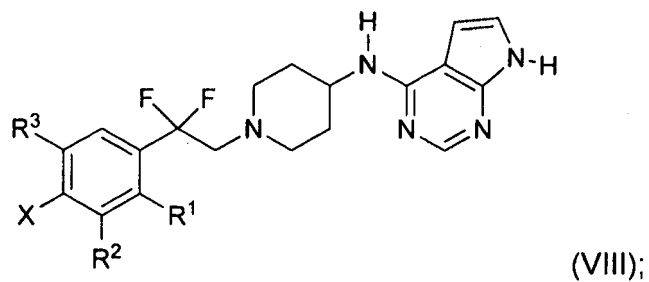
or:
which is a chemical entity of formula (VI):



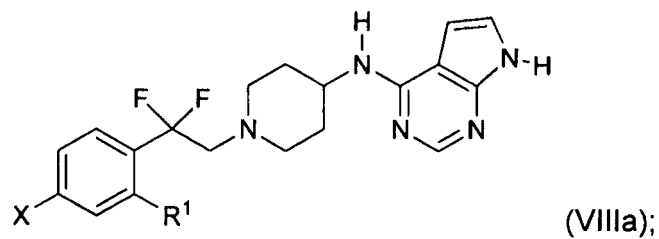
or:
which is a chemical entity of formula (VII):



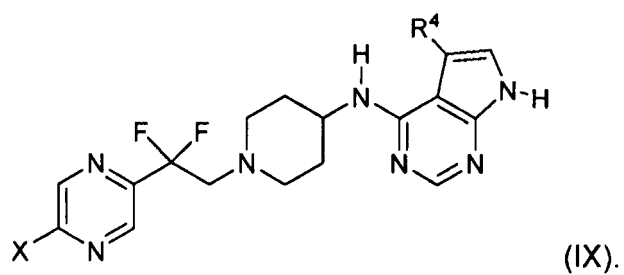
or:
which is a chemical entity of formula (VIII):



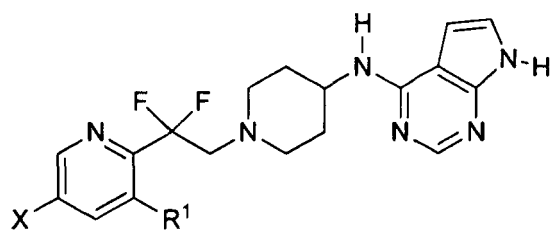
or:
which is a chemical entity of formula (VIIIa):



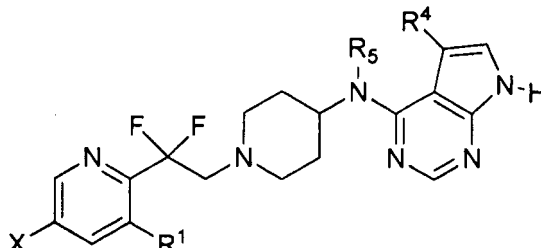
or:
which is a chemical entity of formula (IX):

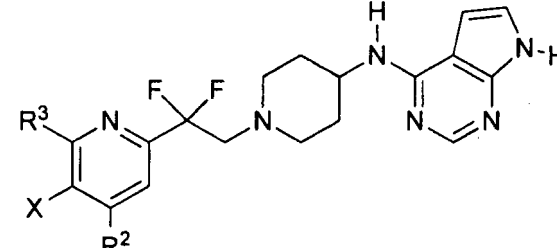


5. The chemical entity of claim 1 selected from the group consisting of:

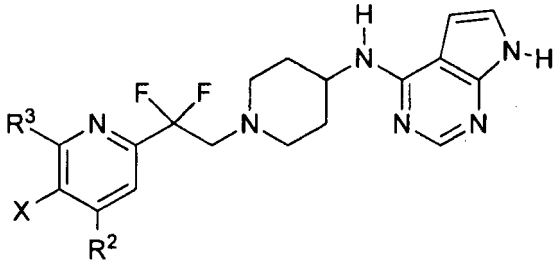


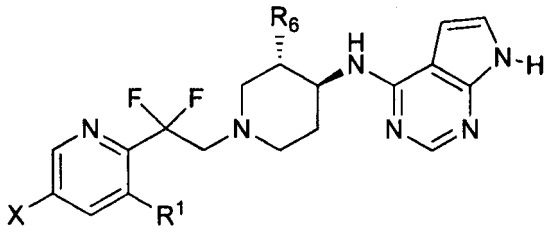
compound	X	R ¹
C-1	H	H
C-2	F	H
C-3	Cl	H
C-4	CH ₃	H
C-5	CF ₃	H
C-6	CF ₂ H	H
C-7	CH ₂ F	H
C-8	CH ₂ CH ₃	H
C-9	cyclopropyl	H
C-10	CH ₃ O	H
C-11	CF ₃ O	H
C-12	CHF ₂ O	H
C-13	SCH ₃	H
C-14	CN	H
C-15	F	F
C-16	Cl	F
C-17	CH ₃	F
C-18	CF ₃	F
C-19	CF ₂ H	F
C-20	CH ₂ F	F
C-21	CH ₂ CH ₃	F
C-22	cyclopropyl	F
C-23	F	Cl
C-24	Cl	Cl
C-25	CH ₃	Cl
C-26	CF ₃	Cl
C-27	cyclopropyl	Cl
C-28	F	CH ₃
C-29	Cl	CH ₃
C-30	CH ₃	CH ₃
C-31	CF ₃	CH ₃
C-32	cyclopropyl	CH ₃

				
compound	X	R ¹	R ⁴	R ⁵
C-33	CF ₃	H	CH ₃	H
C-34	Cl	H	CH ₃	H
C-35	CH ₃	H	CH ₃	H
C-36	CF ₃	H	Cl	H
C-37	Cl	H	Cl	H
C-38	CH ₃	H	Cl	H
C-39	CF ₃	F	CH ₃	H
C-40	Cl	F	CH ₃	H
C-41	CH ₃	F	CH ₃	H
C-42	CF ₃	F	Cl	H
C-43	Cl	F	Cl	H
C-44	CH ₃	F	Cl	H
C-45	CF ₃	H	H	CH ₃
C-46	Cl	H	H	CH ₃
C-47	CH ₃	H	H	CH ₃

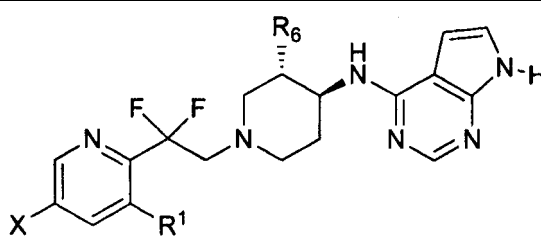
			
compound	X	R ²	R ³
C-48	F	F	H
C-49	Cl	F	H
C-50	CH ₃	F	H
C-51	CF ₃	F	H
C-52	F	CH ₃	H
C-53	Cl	CH ₃	H
C-54	CH ₃	CH ₃	H
C-55	CF ₃	CH ₃	H

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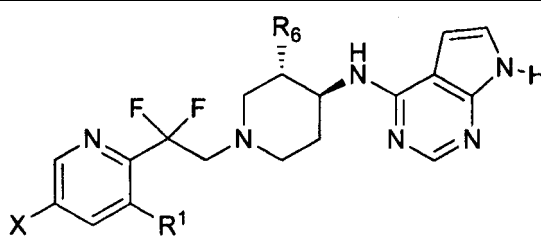
			
compound	X	R ²	R ³
C-56	F	Cl	H
C-57	Cl	Cl	H
C-58	CH ₃	Cl	H
C-59	CF ₃	Cl	F
C-60	F	H	F
C-61	Cl	H	F
C-62	CH ₃	H	F
C-63	CF ₃	H	Cl
C-64	F	H	Cl
C-65	Cl	H	Cl
C-66	CH ₃	H	Cl
C-67	CF ₃	H	CH ₃
C-68	F	H	CH ₃
C-69	Cl	H	CH ₃
C-70	CH ₃	H	CH ₃

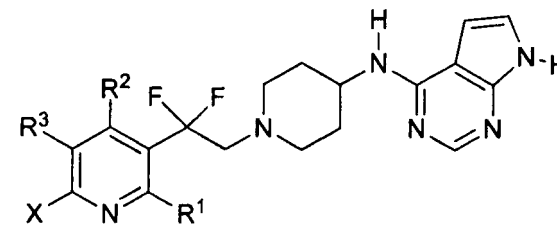
			
compound	X	R ¹	R ⁶
C-71	F	H	CH ₃
C-72	Cl	H	CH ₃
C-73	CH ₃	H	CH ₃
C-74	CF ₃	H	CH ₃
C-75	CF ₂ H	H	CH ₃
C-76	CH ₂ F	H	CH ₃
C-77	OCF ₃	H	CH ₃
C-78	OCF ₂ H	H	CH ₃
C-79	CH ₂ CH ₃	H	CH ₃

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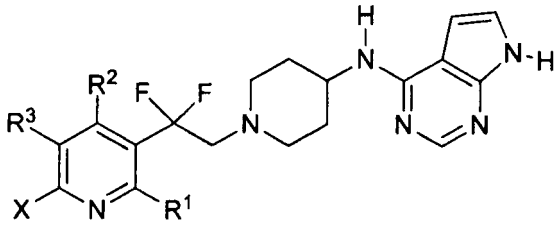
			
compound	X	R ¹	R ⁶
C-80	cyclopropyl	H	CH ₃
C-81	F	H	F
C-82	Cl	H	F
C-83	CH ₃	H	F
C-84	CF ₃	H	F
C-85	CF ₂ H	H	F
C-86	CH ₂ F	H	F
C-87	OCF ₃	H	F
C-88	OCF ₂ H	H	F
C-89	CH ₂ CH ₃	H	F
C-90	cyclopropyl	H	F
C-91	F	F	CH ₃
C-92	Cl	F	CH ₃
C-93	CH ₃	F	CH ₃
C-94	CF ₃	F	CH ₃
C-95	F	F	F
C-96	Cl	F	F
C-97	CH ₃	F	F
C-98	CF ₃	F	F
C-99	F	H	CH ₃
C-100	Cl	H	CH ₃
C-101	CH ₃	H	CH ₃
C-102	CF ₃	H	CH ₃
C-103	CF ₂ H	H	CH ₃
C-104	CH ₂ F	H	CH ₃
C-105	OCF ₃	H	CH ₃
C-106	OCF ₂ H	H	CH ₃
C-107	CH ₂ CH ₃	H	CH ₃
C-108	cyclopropyl	H	CH ₃
C-109	F	H	F
C-110	Cl	H	F
C-111	CH ₃	H	F

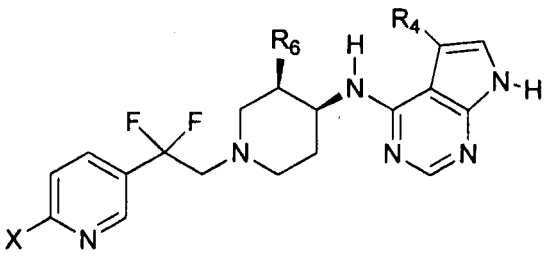
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compound	X	R ¹	R ⁶
C-112	CF ₃	H	F
C-113	CF ₂ H	H	F
C-114	CH ₂ F	H	F
C-115	OCF ₃	H	F
C-116	OCF ₂ H	H	F
C-117	CH ₂ CH ₃	H	F
C-118	cyclopropyl	H	F
C-119	F	F	CH ₃
C-120	Cl	F	CH ₃
C-121	CH ₃	F	CH ₃
C-122	CF ₃	F	CH ₃
C-123	F	F	F
C-124	Cl	F	F
C-125	CH ₃	F	F
C-126	CF ₃	F	F

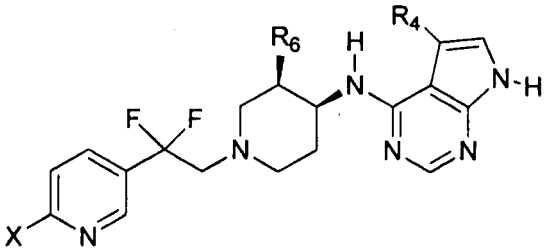
				
compound	X	R ¹	R ²	R ³
C-127	CF ₃	H	H	H
C-128	CH ₃	H	H	H
C-129	F	H	H	H
C-130	Cl	H	H	H
C-131	OCH ₃	H	H	H
C-132	OCF ₃	H	H	H
C-133	SCH ₃	H	H	H
C-134	CH ₂ CH ₃	H	H	H
C-135	cyclopropyl	H	H	H
C-136	CF ₃	F	H	H

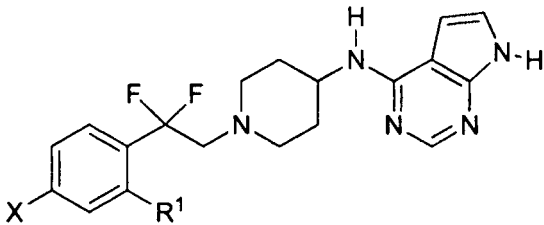
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compound	X	R ¹	R ²	R ³
C-137	CF ₃	H	F	H
C-138	CF ₃	H	H	F
C-139	H	CF ₃	H	H
C-140	H	H	CF ₃	H
C-141	H	H	H	CF ₃

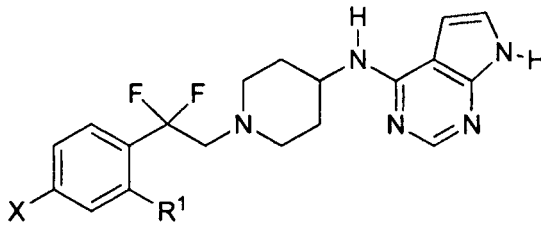
			
compound	X	R ⁴	R ⁶
C-142	CF ₃	CH ₃	H
C-143	CH ₃	CH ₃	H
C-144	CF ₃	H	F
C-145	CH ₃	H	F
C-146	CH ₂ CH ₃	H	F
C-147	SCH ₃	H	F
C-148	cyclopropyl	H	F
C-149	OCF ₃	H	F
C-150	OCH ₃	H	F
C-151	CF ₃	H	CH ₃
C-152	CH ₃	H	CH ₃
C-153	CH ₂ CH ₃	H	CH ₃
C-154	SCH ₃	H	CH ₃
C-155	cyclopropyl	H	CH ₃
C-156	OCF ₃	H	CH ₃
C-157	OCH ₃	H	CH ₃
C-158	CF ₃	Cl	H
C-159	CH ₃	Cl	H
C-160	CF ₃	H	F

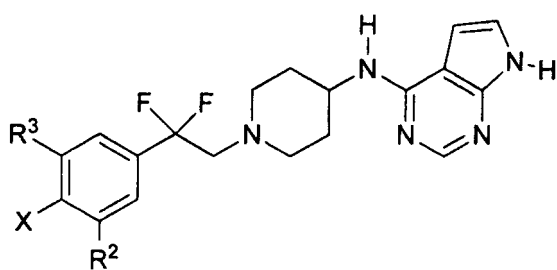
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compound	X	R ⁴	R ⁶
C-161	CH ₃	H	F
C-162	CH ₂ CH ₃	H	F
C-163	SCH ₃	H	F
C-164	cyclopropyl	H	F
C-165	OCF ₃	H	F
C-166	OCH ₃	H	F
C-167	CF ₃	H	CH ₃
C-168	CH ₃	H	CH ₃
C-169	CH ₂ CH ₃	H	CH ₃
C-170	SCH ₃	H	CH ₃
C-171	cyclopropyl	H	CH ₃
C-172	OCF ₃	H	CH ₃
C-173	OCH ₃	H	CH ₃

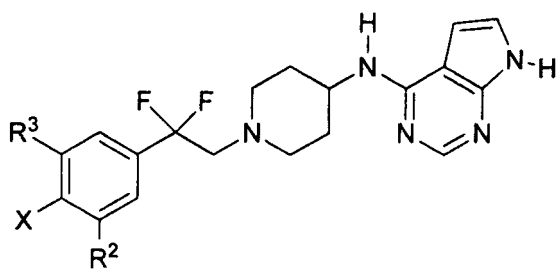
		
compound	X	R ¹
C-174	H	H
C-175	F	H
C-176	Cl	H
C-177	CH ₃	H
C-178	CF ₃	H
C-179	CF ₂ H	H
C-180	CH ₂ F	H
C-181	CH ₂ CH ₃	H
C-182	cyclopropyl	H
C-183	CH ₃ O	H
C-184	CF ₃ O	H

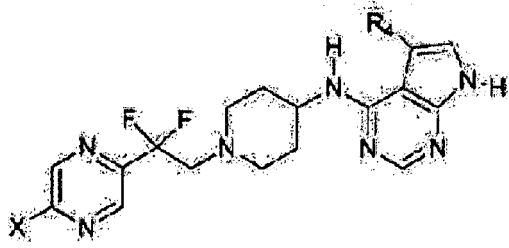
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compound	X	R ¹
C-185	CHF ₂ O	H
C-186	SCH ₃	H
C-187	CN	H
C-188	F	F
C-189	Cl	F
C-190	CH ₃	F
C-191	CF ₃	F
C-192	CF ₂ H	F
C-193	CH ₂ F	F
C-194	CH ₂ CH ₃	F
C-195	cyclopropyl	F
C-196	F	Cl
C-197	Cl	Cl
C-198	CH ₃	Cl
C-199	CF ₃	Cl
C-200	cyclopropyl	Cl
C-201	F	CH ₃
C-202	Cl	CH ₃
C-203	CH ₃	CH ₃
C-204	CF ₃	CH ₃
C-205	cyclopropyl	CH ₃

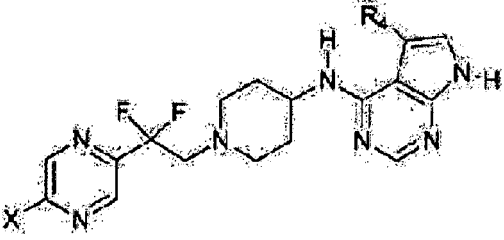
			
compound	X	R ²	R ³
C-206	F	F	H
C-207	Cl	F	H

(continued)

			
compound	X	R ²	R ³
C-208	CH ₃	F	H
C-209	CF ₃	F	H
C-210	F	CH ₃	H
C-211	Cl	CH ₃	H
C-212	CH ₃	CH ₃	H
C-213	CF ₃	CH ₃	H
C-214	F	Cl	H
C-215	Cl	Cl	H
C-216	CH ₃	Cl	H
C-217	CF ₃	Cl	F
C-218	F	H	F
C-219	Cl	H	F
C-220	CH ₃	H	F
C-221	CF ₃	H	Cl
C-222	F	H	Cl
C-223	Cl	H	Cl
C-224	CH ₃	H	Cl
C-225	CF ₃	H	CH ₃
C-226	F	H	CH ₃
C-227	Cl	H	CH ₃
C-228	CH ₃	H	CH ₃

		
compound	X	R ⁴
C-229	CF ₃	H

(continued)

		
compound	X	R ⁴
C-230	CH ₃	H
C-231	Cl	H
C-232	F	H
C-233	CF ₂ H	H
C-234	OCF ₃	H
C-235	OCF ₂ H	H
C-236	CH ₂ CH ₃	H
C-237	cyclopropyl	H
C-238	isopropyl	H
C-239	CH ₃	CH ₃
C-240	CH ₃	CH ₃
C-241	CH ₂ CH ₃	CH ₃
C-242	cyclopropyl	CH ₃
C-243	isopropyl	CH ₃
C-244	OCF ₃	CH ₃

6. A pharmaceutical composition comprising the chemical entity of any one of claims 1 to 5 and a pharmaceutically acceptable carrier.
7. The pharmaceutical composition of claim 6 for oral administration.
8. The chemical entity of any one of claims 1 to 5 for use in treating a disease or disorder responsive to NR2B.
9. The chemical entity for use of claim 8, wherein the disease or disorder is depression, a seizure disorder, pain, a movement disorder Huntington's disease, cognitive, dysfunction, cerebral ischaemia, traumatic brain injury, or a substance abuse disorder.
10. The chemical entity for use of claim 9, wherein the disease or disorder is depression.
11. Use of the chemical entity of any one of claims 1 to 5 in the manufacture of a medicament for treating a disease or disorder responsive to NR2B.
12. The use of claim 11, wherein the disease or disorder is depression, a seizure disorder, pain, a movement disorder Huntington's disease, cognitive, dysfunction, cerebral ischaemia, traumatic brain injury, or a substance abuse disorder.
13. The use of claim 12, wherein the disease or disorder is depression.