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CNS Permeability of Drugs Predicted by a Decision Tree

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Table 1. Comparison of experimental and predicted CNS activity for the training set

compound	observed CNS activity	predicted CNS activity
abecarnil	+	–
acarbose	–	–
acetone	+	+
acrivastine	–	–
alclofenac	–	–
alprenolol	–	–
amantadine	+	+
amiodarone	–	–
amobarbital	+	+
ampicilline	–	–
apomorphine	+	+
asimadoline	–	–
astemizole	–	–
atenolol	–	–
baclofen	+	+
BBcpd14 [112598-32-0]	+	+
benzene	+	+
betaxolol	–	–
biperidine	+	+
bufuralol	–	–
butanone	+	+
captopril	–	–
carbidopa	–	–
carebastine	–	–
carmoxirol	–	–
cefetamet pivoxil	–	–
ceftriaxone	–	–

cephalexin	–	–
cephalotin	–	–
cetirizine	–	–
CGS-19755 [110347-85-8]	+	+
chloramphenicol	–	–
cimetidine	–	–
cisapride	–	–
chlordiazepoxide	+	+
clobazam	+	+
clofibric acid	–	–
clomipramine	+	+
clonazepam	+	+
clozapine	+	+
chlorprothixene	+	+
corticosterone	–	–
coumarin	–	–
carbenicillin	–	–
cyclobarbital	+	+
demeclocycline	–	–
dexamethasone	–	–
diazepam	+	+
diltiazem	–	–
diphenhydramine	+	+
dizocilpine	+	+
domperidone	–	–
dopamine	+	+
doxepine	+	+
doxylamine	+	+
ebastine	–	–
elacridar	–	–
estradiol valerate	–	–
ethinyl estradiol	–	–
ethyl ether	+	+
felbamate	+	+

felodipine	–	–
fenoprofen	–	–
fentanyl	+	+
FK-506 (fujimycin)	–	–
fleroxacine	–	–
flumazenil	+	+
flunitrazepam	+	+
fluoxetine	+	+
flupentixol	+	+
flurazepam	+	+
fluroxene	+	+
fluvastatin	–	–
furosemide	–	–
gabapentin	+	+
GCP-37849 [127510-31-0]	+	+
GCP-39551 [127910-32-1]	+	+
guanabenz	–	–
guanfacine	–	–
GYKI-52466 [102771-26-6]	+	+
haloperidol	+	+
hexane	+	+
hydroxypethidine	+	+
ICI-204448 [121264-04-8]	–	–
ifenprodil	+	–
isotretinoin	–	–
isradipine	+	+
ketamine	+	+
ketoprofen	–	–
labetalol	–	–
lamotrigine	+	+
lidocaine	+	+
loperamide	–	–
loratadine	–	–
lorazepam	+	+

lorcainide	+	+
D-mannitol	–	–
2,2-dimethylbutane	+	+
mecoprop	+	+
mefenidil	+	+
meprobamate	+	+
mequitazine	+	+
metoprolol	–	–
mexiletine	+	+
mibefradil	–	–
miglitol	–	–
milacemide	+	+
minoxidil	–	+
morphine	+	+
nadolol	–	–
naloxone	+	+
naltrexone	+	+
naproxen	–	–
napsagatran	–	–
neostigmine bromide	–	–
nifedipine	+	+
nitrazepam	+	+
nitrendipine	–	–
N-methylnaltrexone chloride	–	–
norfenefrine	–	–
nortriptyline	+	+
noxiptilin	+	+
olsalazine	–	–
orphenadrine	+	+
oxcarbazepine	+	+
oxprenolol	–	–
PD-117302 [111728-01-9]	+	+
penicillin G	–	–
perphenazine	+	+

phaclofen	+	+
phenacetin	–	+
phenobarbital	+	+
pheniramin	–	+
piracetam	+	+
pirenzepine	–	–
practolol	–	–
pravastin	–	–
procylidine	+	+
prednisolone	–	–
prednisone	–	–
primidone	+	+
probenecid	–	–
progabide	+	+
promethazine	+	+
propranolol	–	–
proscillaridin	–	–
quinpirole	+	+
quipazine	+	+
raclopride	+	+
ralitoline	+	+
remacemide	+	+
remikiren	–	–
roxindole	+	+
saclofen	+	+
salbutamol	–	–
SCH-23390 [87075-17-0]	+	+
spiradoline	+	+
stiripentol	+	+
sulfasalazine	–	–
sulpiride	+	+
sumatriptan	–	–
taltrimide	+	+
tamitinol	+	+

teflurane	+	+
temafloxacin	–	–
terbutaline	–	–
terfenadine	–	–
testosterone	+	+
trifluoperazine	+	+
thiopental	+	+
tiacrilast	–	–
tiagabine	+	+
tifluadom	+	+
tocainide	–	+
tolamolol	–	–
toliprolol	–	–
topiramate	+	+
tranylcypromine	+	+
triazolam	+	+
U-50488 [67198-13-4]	+	+
valproate pivoxil	+	+
vigabatrin	+	+
S-warfarin	–	+
zimeldine	+	+
zolmitriptan	+	+
zonisamide	+	+

Table 2. Comparison of experimental and predicted CNS activity for the test set

compound	observed CNS activity	predicted CNS activity
acetylsalicylic acid	+	+
acetaminophen	+	+
amitriptyline	+	+
chloroform	+	+
1,1,1-trichloroethan	+	+
clonidine	+	+
carbamazepine	+	+
didanosine	–	+
enflurane	+	+
ethanol	+	+
halothane	+	+
heptane	+	+
hydrocortisone	–	–
icotidine	–	–
imipramine	+	+
indinavir	–	–
indomethacin	–	–
isoflurane	+	+
lupitidine	–	–
mianserin	+	+
mepyramine	+	+
methadone	+	+
pentane	+	+
quinidine	–	+
ranitidine	–	–
risperidone	+	–
salicylic acid	–	+
ropinirole (SKF-101468)	+	+
SKF-89124 [81654-62-8]	+	+
temelastine	–	–

thioperamide	+	+
tibolone	+	–
tiotidine	–	–
toluene	+	+
trichloroethylene	+	+
valproic acid	+	+
zidovudine	–	+
zolantidine	+	+

Table 3. Computed molecular descriptors

descriptor class	number of descriptors	descriptors
simple molecular properties	14	molecular weight, number of hydrogen-bond donors and acceptors, element counts, number of rotatable bonds, number of aromatic five and six-membered rings, number of COOH, NR_3, and NO_2 groups
molecular connectivity, topology,	49	Kier & Hall χ indices, Kier and Hall κ indices, Kier flexibility, E-states, Zagreb and Wiener index, path lengths between hydrogen-bonding atoms, molecular distance edge terms, hybridization and substitution on carbon atoms
geometrical properties	14	molecular volume, principal components of the molecular geometry, globularity, geometric E-states, gravitational indices
quantum chemical properties	40	dipole moment, ionization potential, E(HOMO), E(LUMO), ΔE(HOMO-LUMO), dipolar density, mean polarizability, electrostatic and covalent hydrogen-bond acidity and basicity, electrostatic potential derived atomic charges, sum of atomic charges on elements, topological electronic indices, statistics of the electrostatic potential, fractional polar surface areas

Table 4. Actual descriptors used at branching points in the decision tree shown in Fig. 1

variable	descriptor definition	reference (see below)
PCGC	1st principal component of molecular geometry	[1]
QSUMO	sum of atomic charges on oxygen atoms	[2]
COOH	number of carboxylic acid groups	–
VXBAL	total variance of ESP · balance parameter	[3]
MPOLAR	molecular polarizability	[4]
HBDON	number of hydrogen-bond donors	–
HLSURF	ratio of surface on halogen atoms to total surface	this study
DIPDENS	dipolar density	[5]
QSUM–	sum of negative ESP charges	[6]
QSUM+	sum of positive ESP charges	[6]
DIPM	dipole moment (from the density matrix)	[1]
AR5	number of aromatic 5-membered rings	[1]
C2SP1	number of triply bound carbons bound to two other carbons	–
KAP2A	Kier & Hall $^{2}\kappa_{\alpha}$ index	[7, 8]
KAP3A	Kier & Hall $^{3}\kappa_{\alpha}$ index	[7, 8]
MDE13	molecular distance-edge vector λ_{13}	[9]
MDE34	molecular distance-edge vector λ_{34}	[9]

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