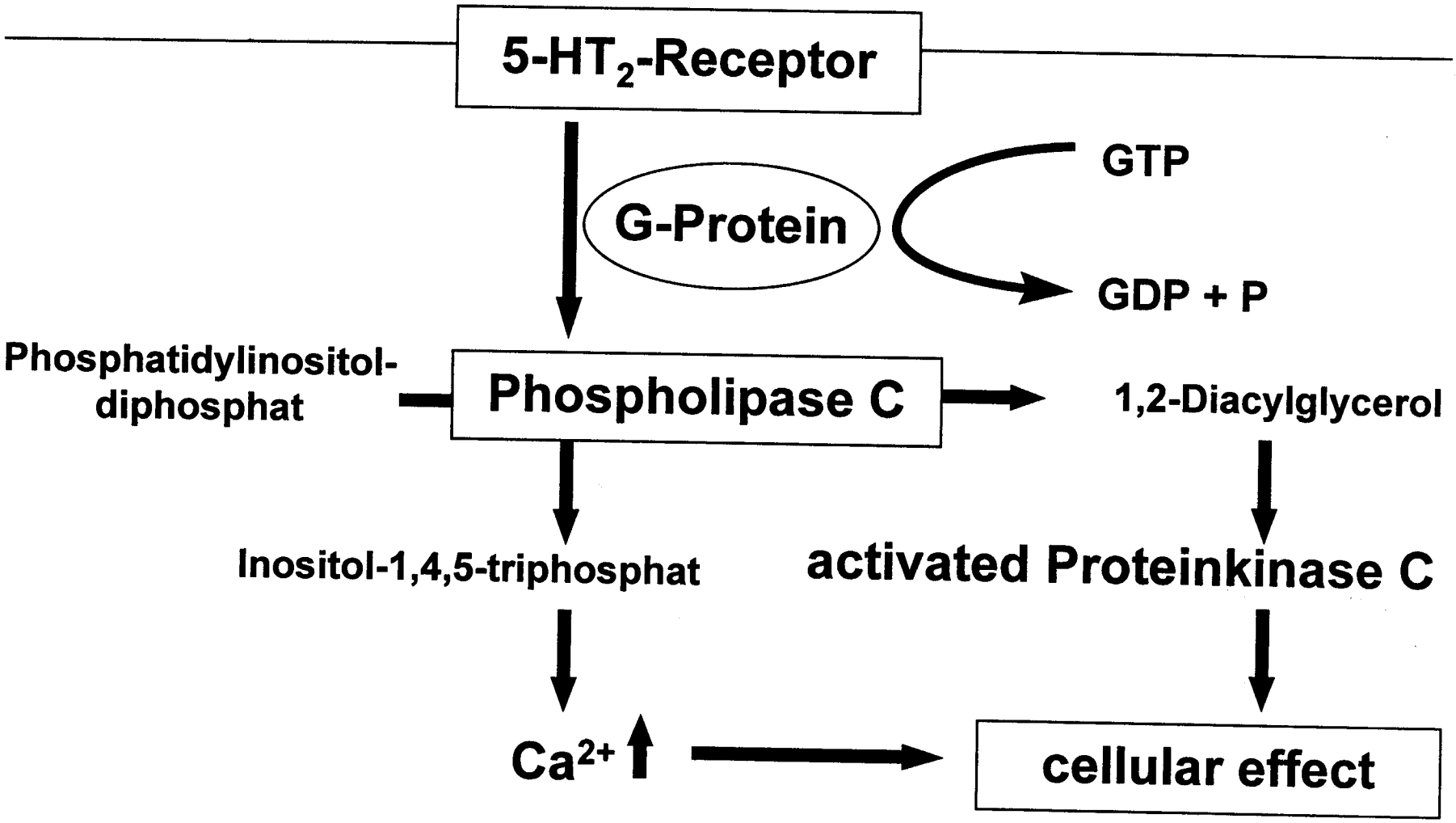
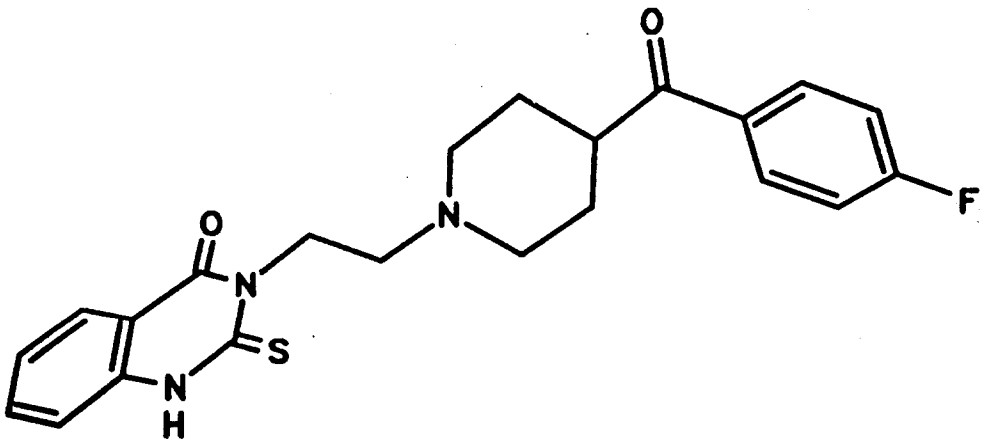
A Molecular Modelling study on the serotoninergic $5HT_{2A}$-receptor

GPCR Mechanism

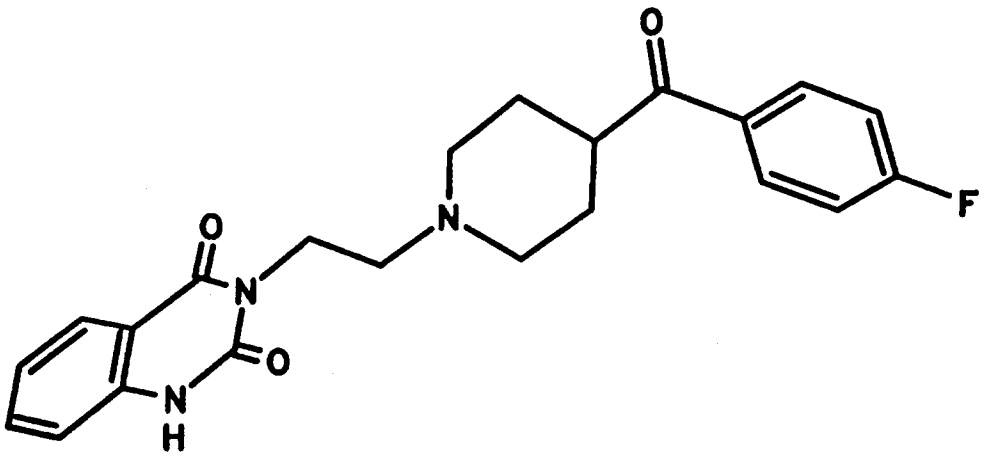


5-HT_2 ANTAGONISTS

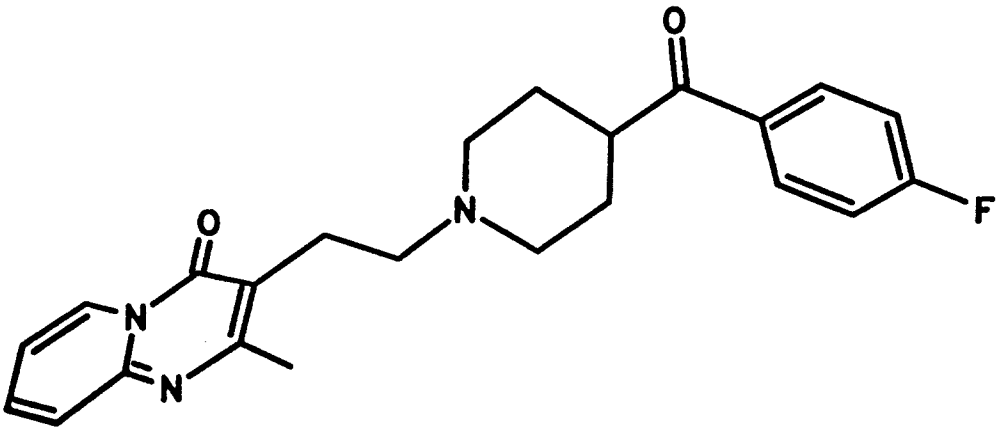
Butyrophenone derivatives	Spiperone Spirilene Pipamperone
Ketanserin derivatives	Altanserin Ritanserin Ketanserin R 56413 Pirenperone Butanserin SM 9018 MDL 11939
Tricyclic compounds	Methiothepin Clotiapin Zotepin Chlorpromazine Irindalone Mianserin Clopipazan Cyproheptadine
Miscellanous	Emopamil Xylamidine ICI 169369
Ergolines	not under study



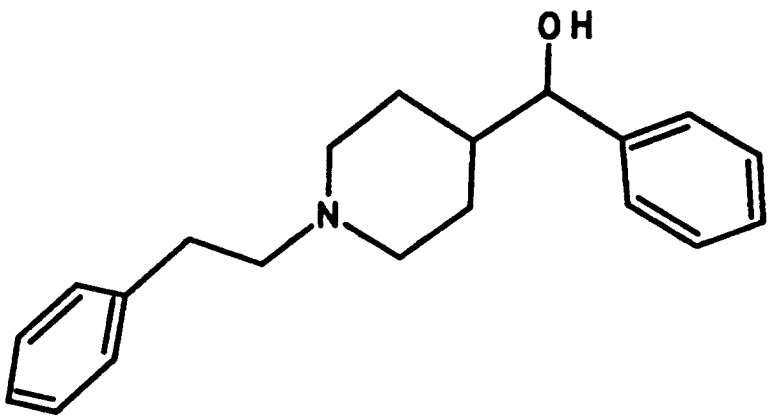
altanserin



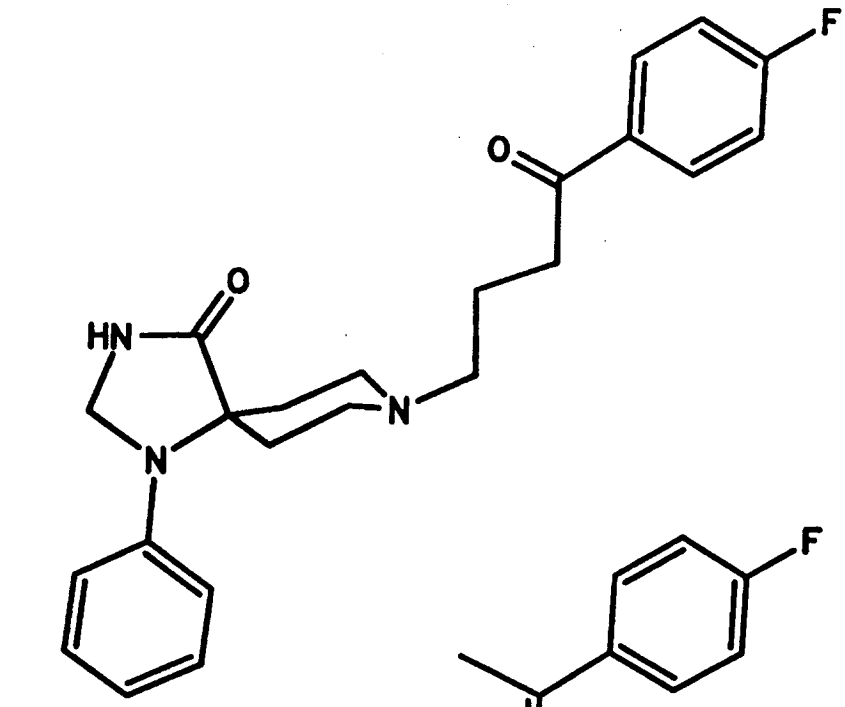
ketanserin



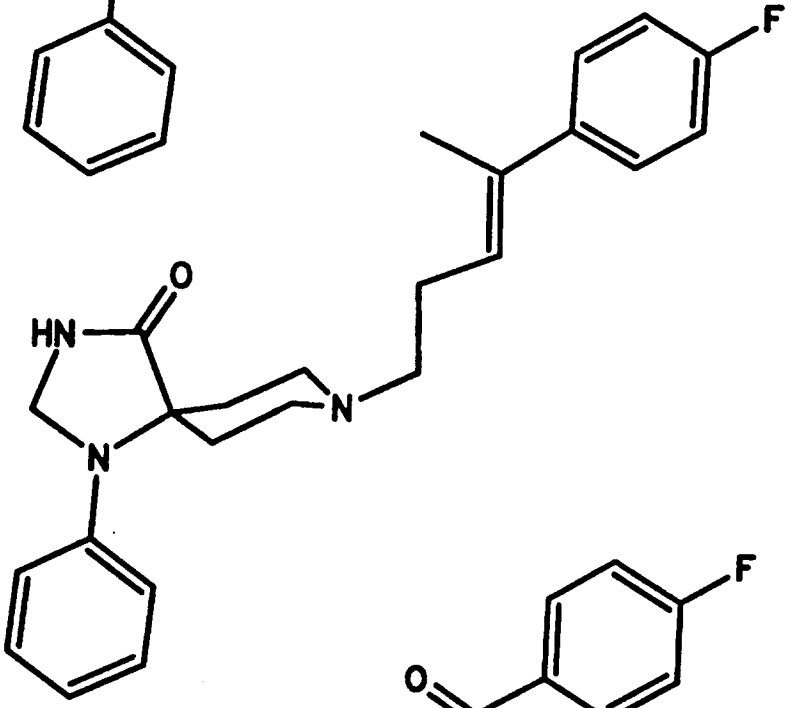
pirenperone



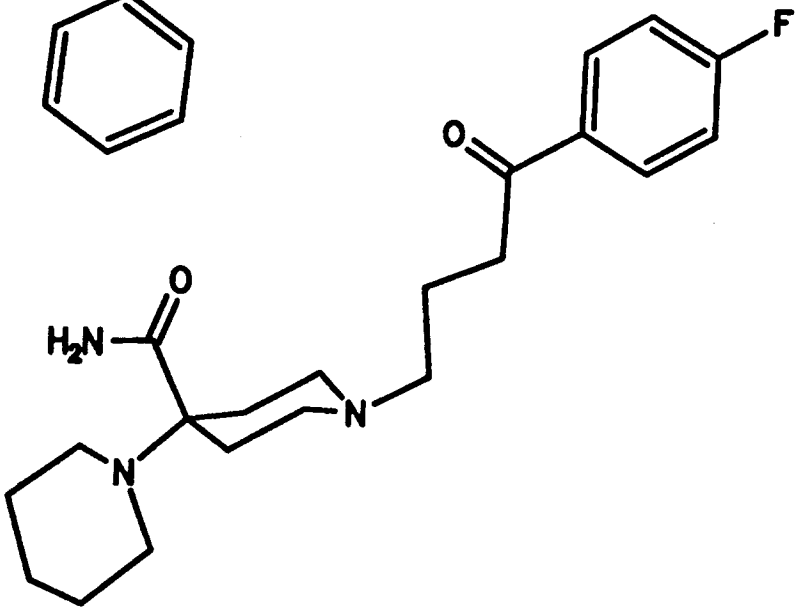
mdl 11939



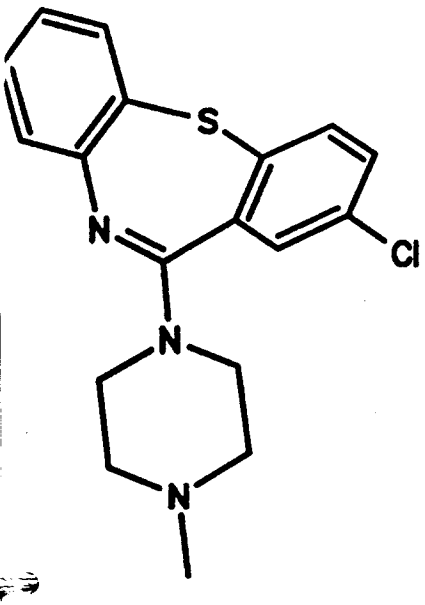
spiperone



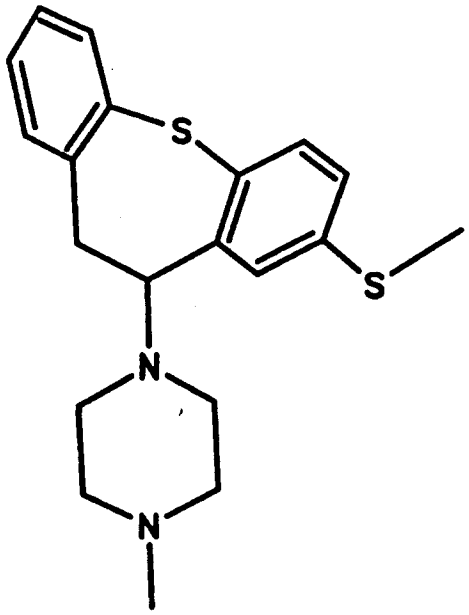
spirilene



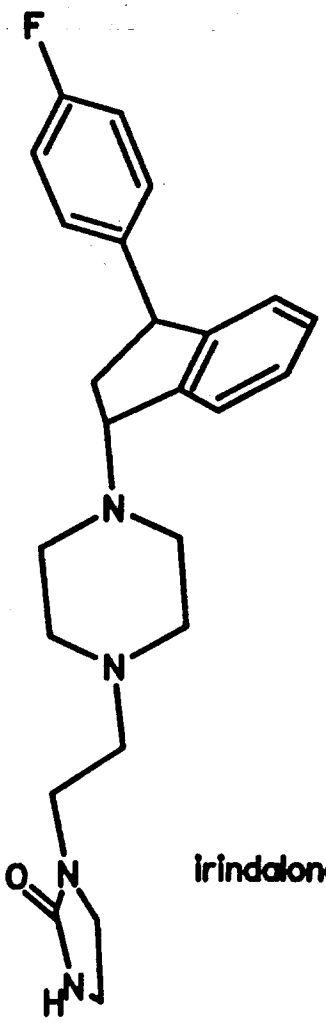
pipamperone



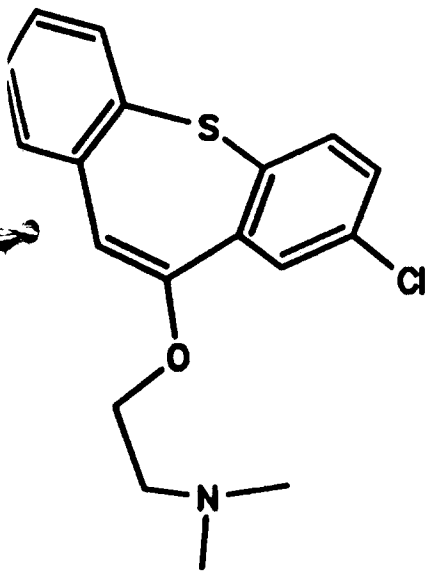
clotiapin



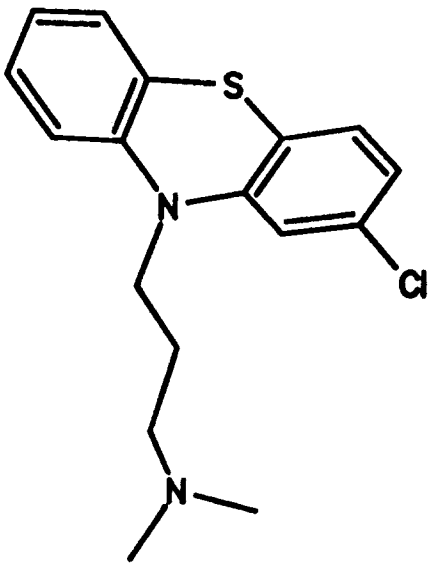
methiotepine



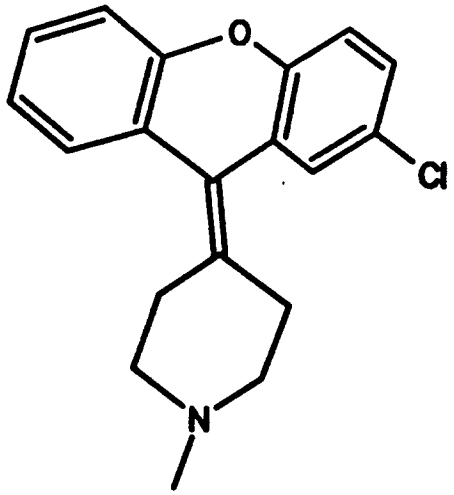
irindalone



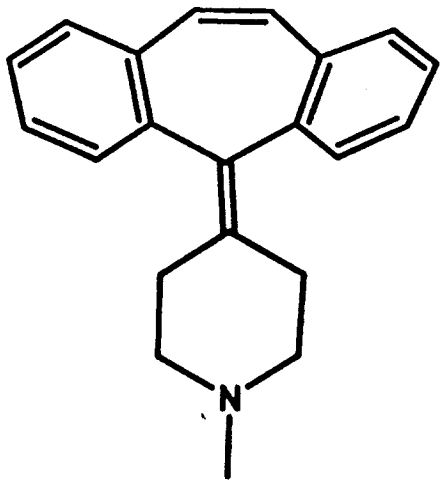
zotepin



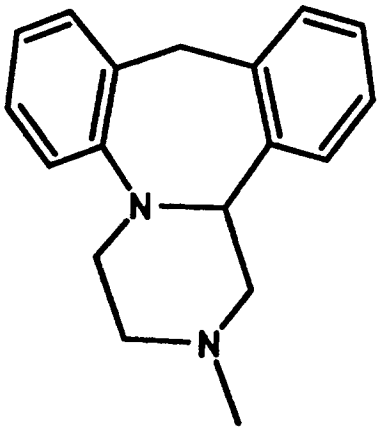
chlorpromazine



clopipazan



cyproheptadine



mianserin

What a Pharmacophore is

A pharmacophore is the specific 3-dimensional arrangement of structural elements of a drug molecule, necessary for recognition and binding at the receptor.

Pharmacophore Determination

1. Conformational Analysis

2. Molecular Electrostatic Potentials

3. Molecular Interaction Fields

Conformational Analysis

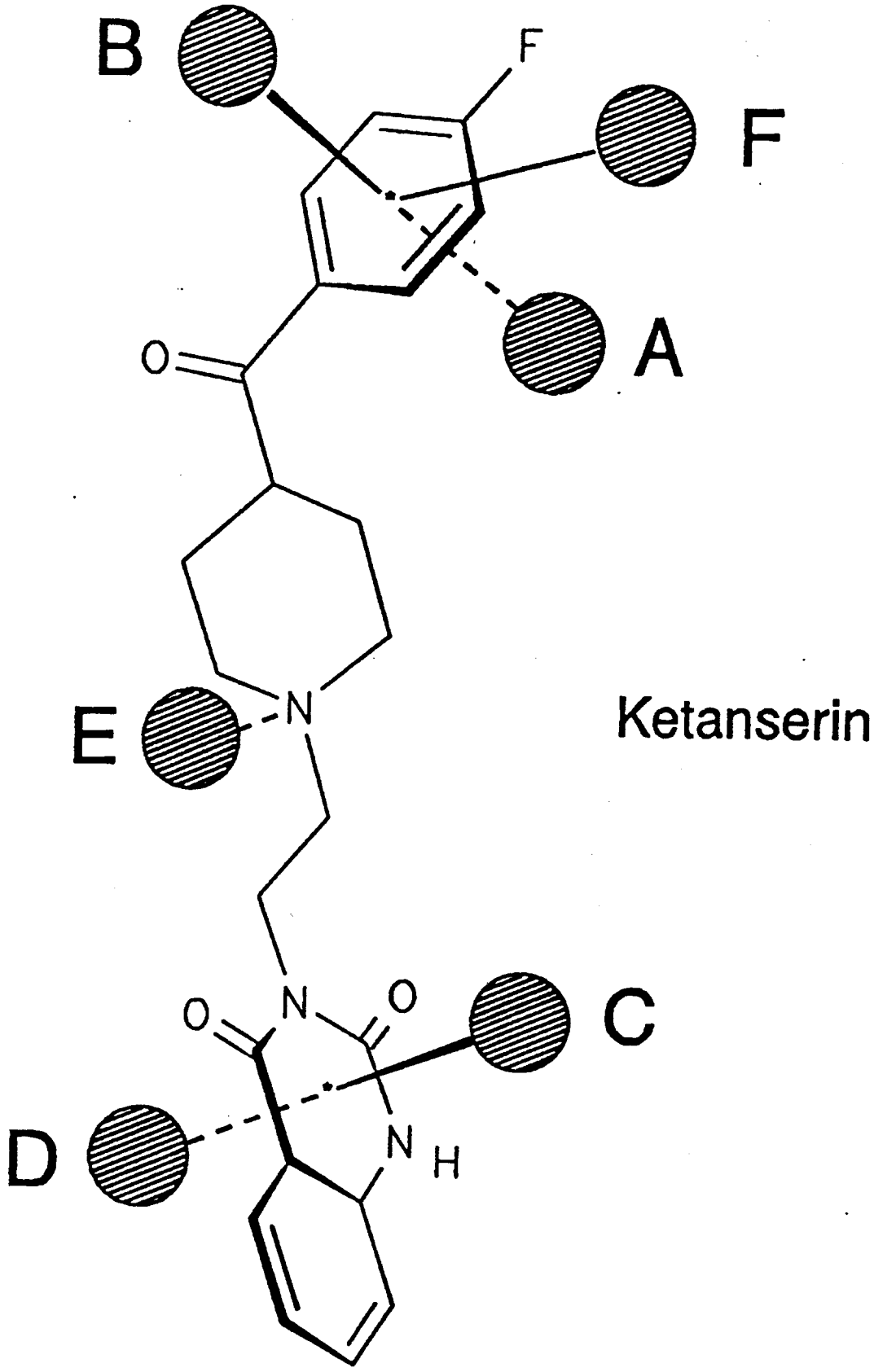
Search for common sterical properties

Molecular Electrostatic Potentials

Search for common electronical properties

Molecular Interaction Fields

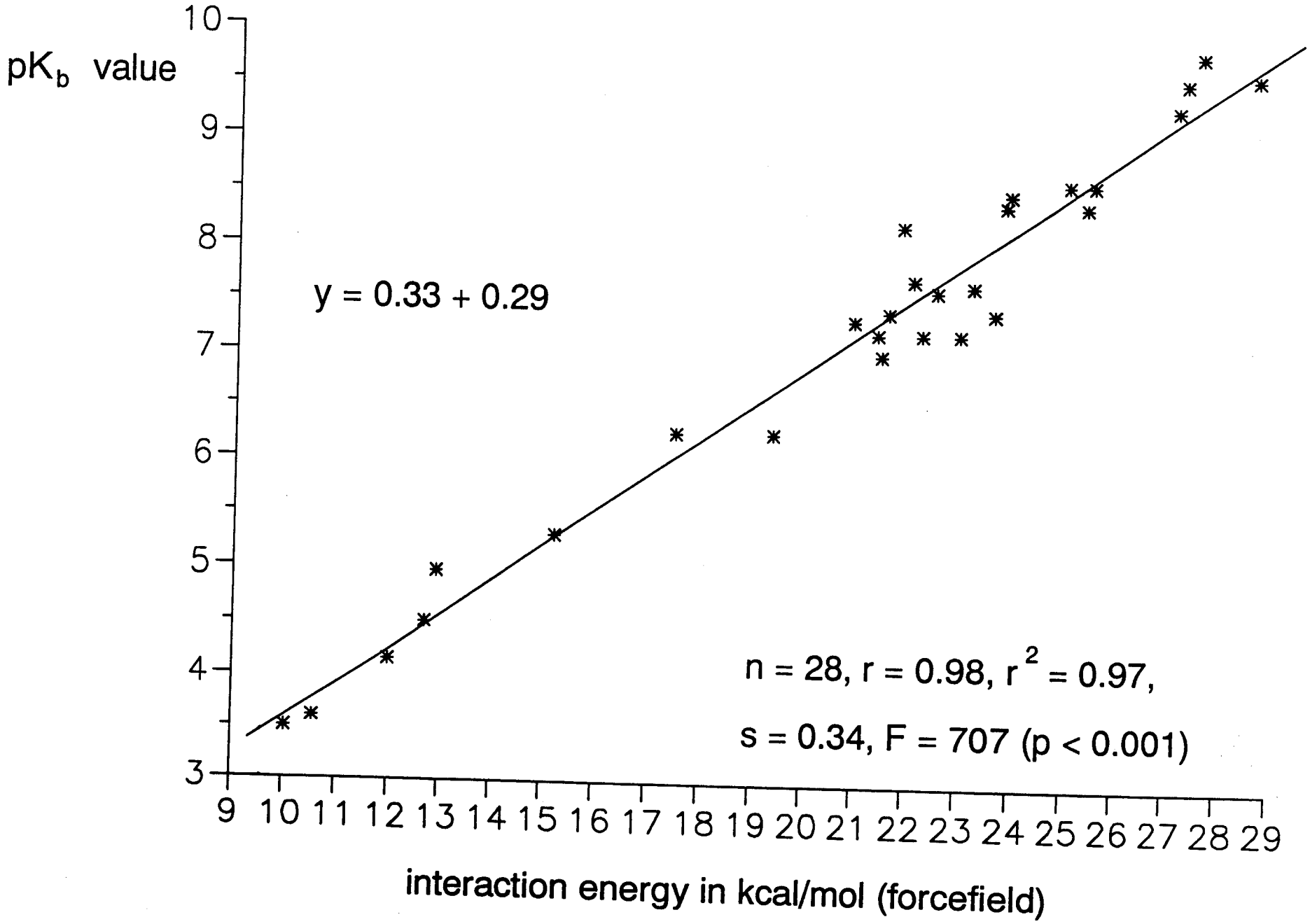
Calculation of potential interactions with binding partners

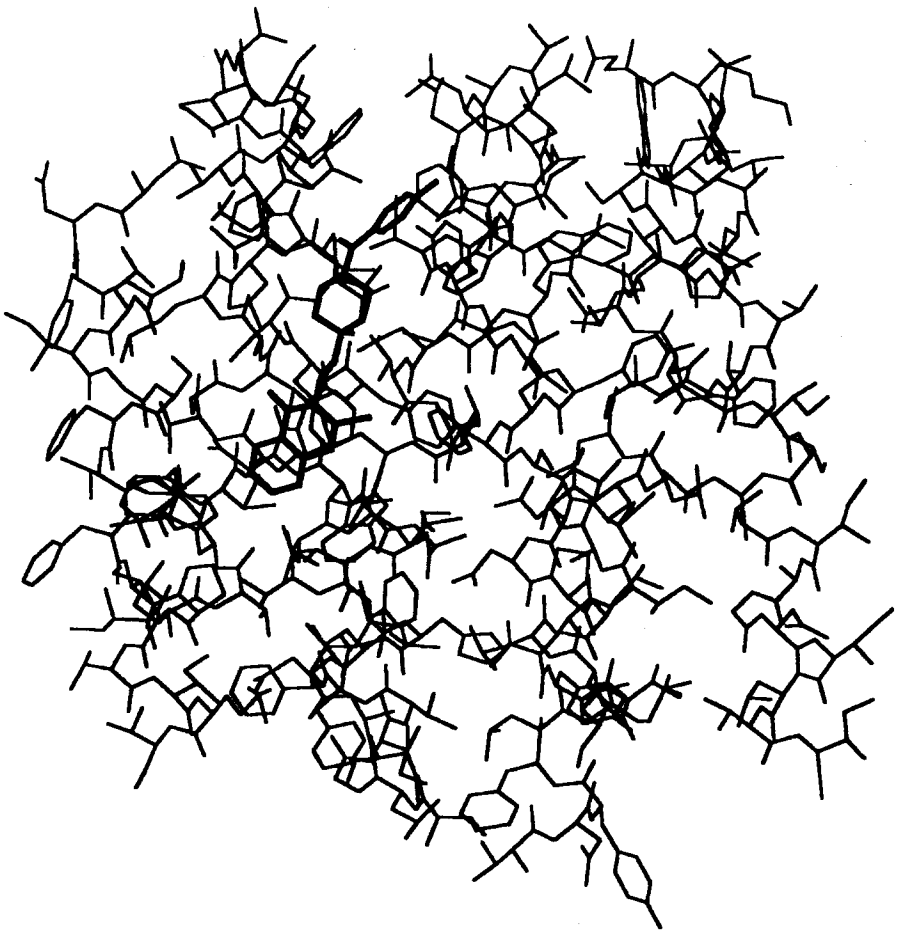


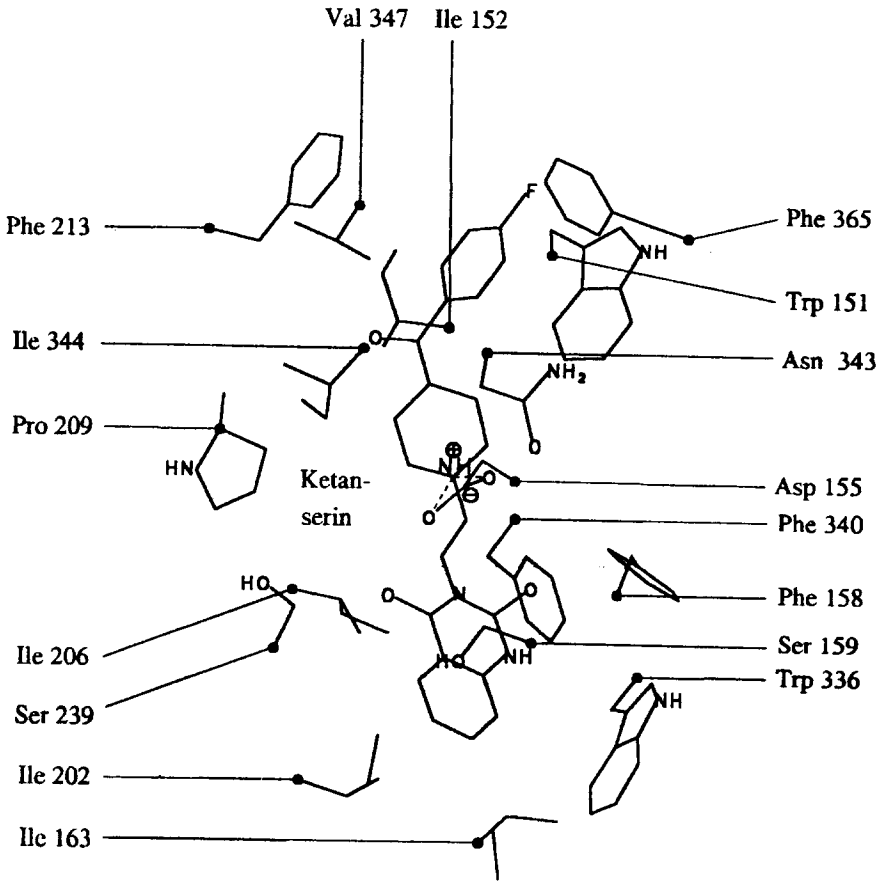
Ketanserin

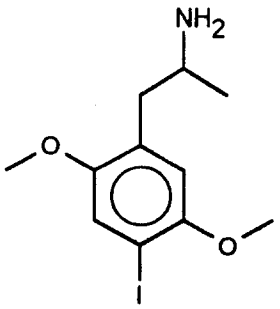
Validation of the model

Calculated interaction energies significantly correlate with experimental binding affinities


pK$_b$ value
10
9
8
7
6
5
4
3
y = 0.33 + 0.29
n = 28, r = 0.98, r^2 = 0.97,
s = 0.34, F = 707 (p < 0.001)
9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
interaction energy in kcal/mol (forcefield)

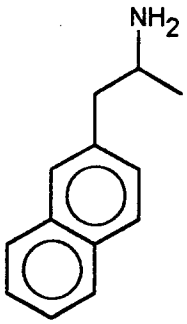



Val 347
Ile 152
Phe 213
Phe 365
Trp 151
Ile 344
Asn 343
Pro 209
Ketan-
serin
Asp 155
Phe 340
Phe 158
Ser 159
Trp 336
Ile 206
Ser 239
Ile 202
Ile 163



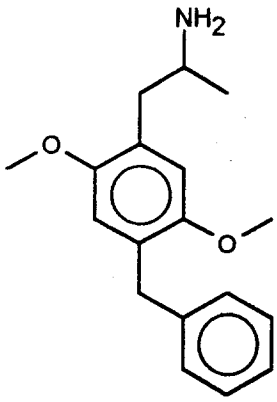
R-(2,5-Dimethoxy-4-iod-phenyl)-2-propanamin

kurz: R-DOI



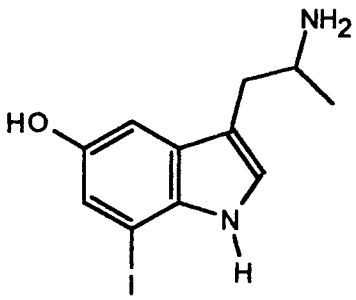
R-Naphtyl-2-propanamin

kurz: 1-NAP



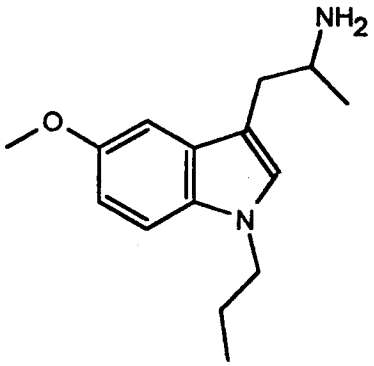
R-(2,5-Dimethoxy-4-benzyl-phenyl)-2-propanamin

kurz: R-BZDO



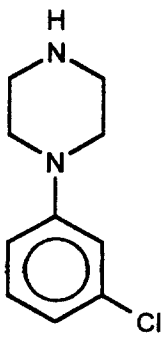
S-(7-Iod-5-hydroxy)-α-methyltryptamin

kurz: S-IHMT



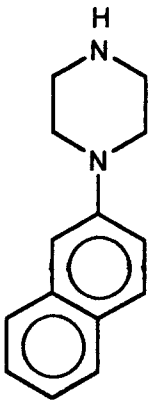
S-(1-Propyl-5-methoxy)-α-methyltryptamin

kurz: S-PMMT



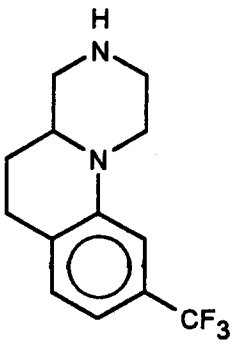
(3-Chlorphenyl)-piperazin

kurz: MCPP



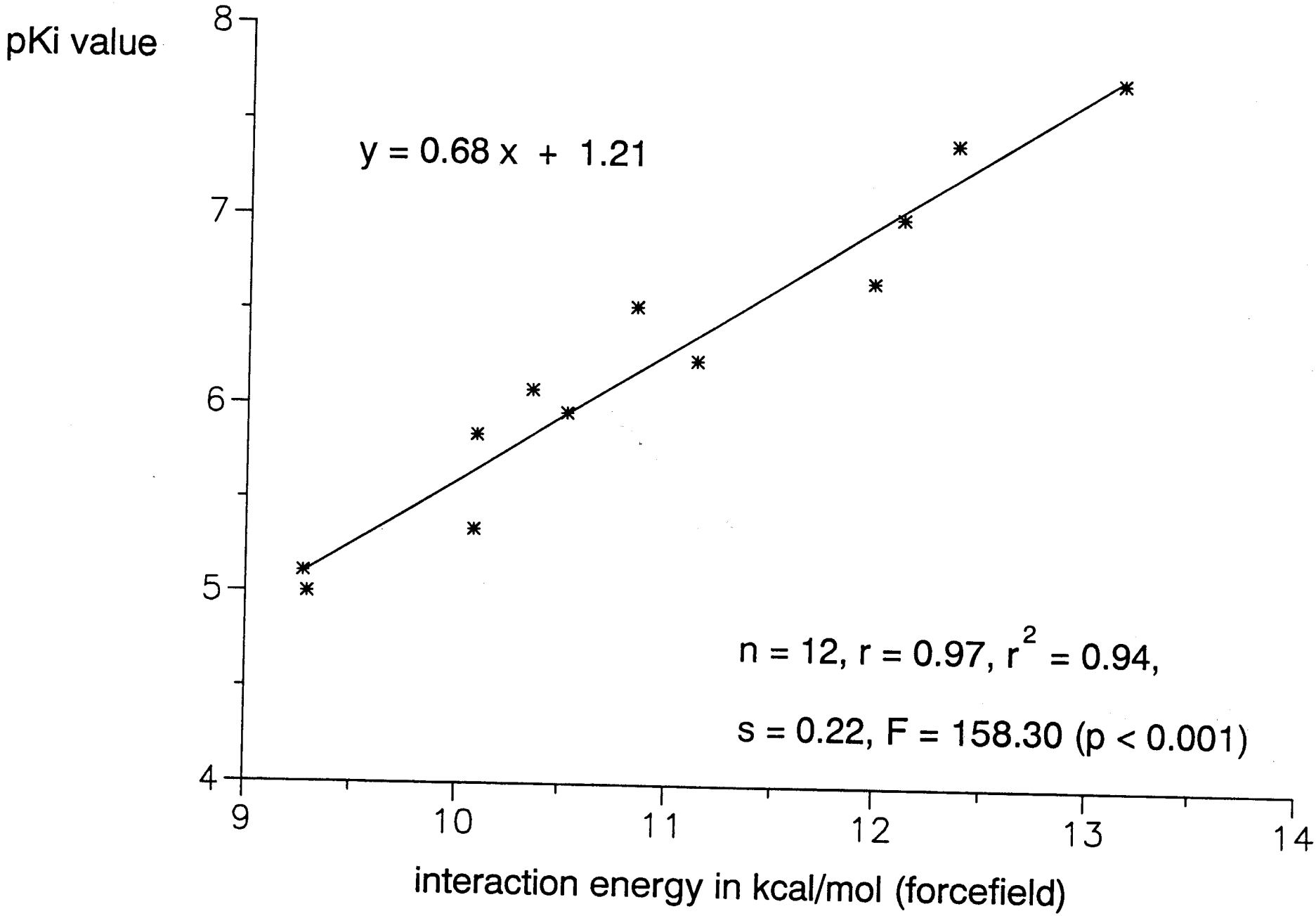
(2-Naphthyl)-piperazin

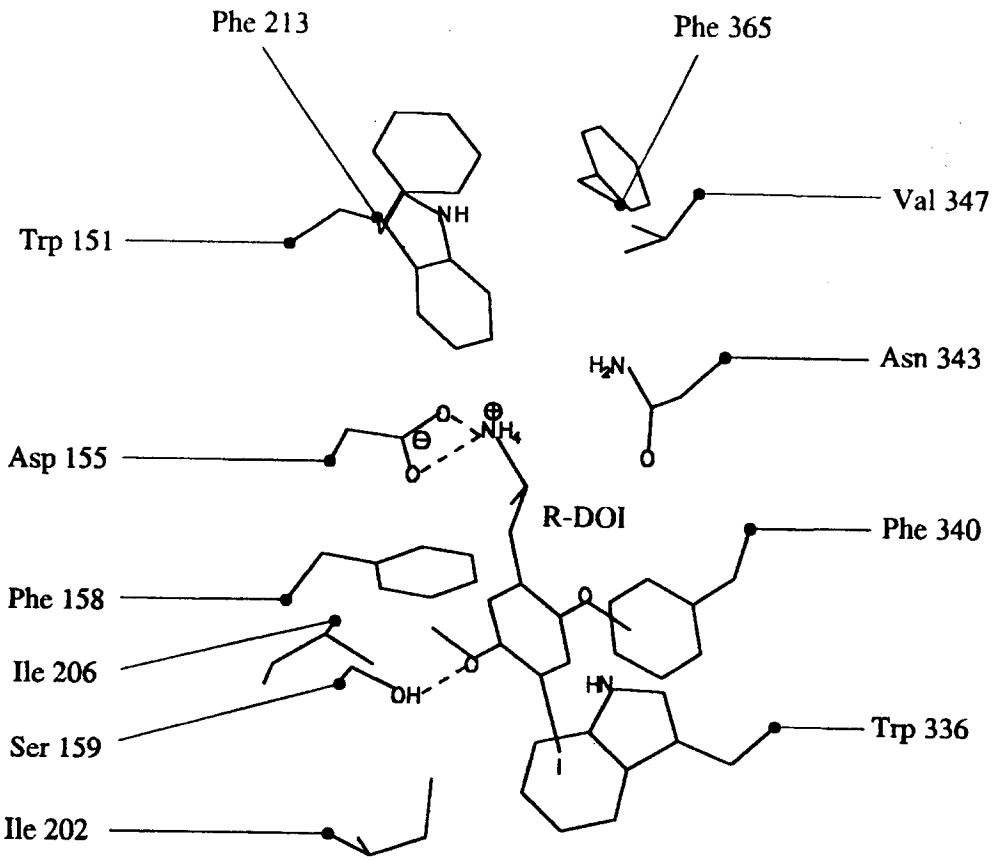
kurz: 1-NP

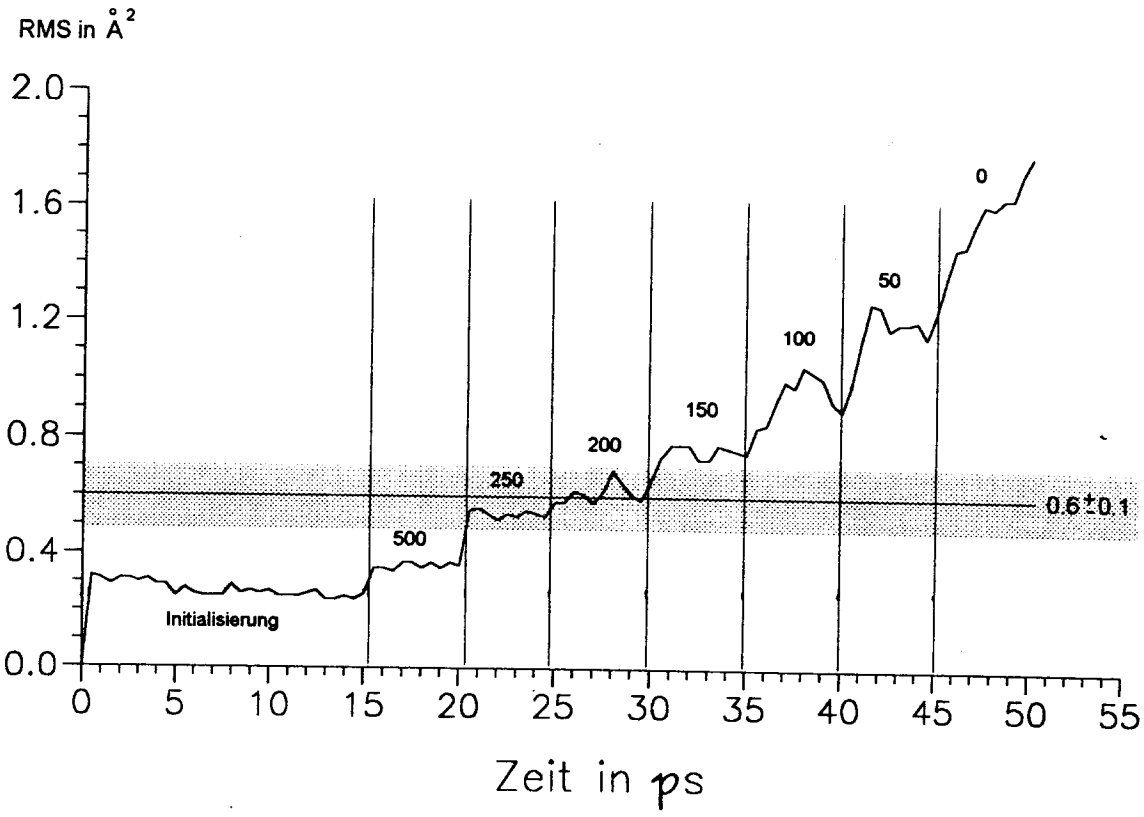


2,3,4,4a,5,6-Hexahydro-9-(trifluormethyl)-1H-pyrazinol [1,2-a]-chinolin

kurz: HTPC


pKi value
8
7
6
5
4
y = 0.68 x + 1.21
n = 12, r = 0.97, r 2 = 0.94,
s = 0.22, F = 158.30 (p < 0.001)
9
10
11
12
13
14
interaction energy in kcal/mol (forcefield)


Phe 213
Phe 365
Val 347
Trp 151
NH
Asn 343
Asp 155
R-DOI
Phe 340
Phe 158
Ile 206
OH
Ser 159
HN
Trp 336
Ile 202


RMS in Å²
2.0
1.6
1.2
0.8
0.4
0.0
0
5
10
15
20
25
30
35
40
45
50
55
Zeit in ps
Initialisierung
500
250
200
150
100
50
0
0.6±0.1

Acknowledgements

Molecular Modelling

Dr. H. Briem

Dr. U. Jendretzki

Synthesis and Pharmacology

Dr. S. Elz

Institut für Pharmazie, FU Berlin