

Action of benzimidazolo-piperazinyl derivatives on dopamine receptors

Zenish J. Jain · Rani S. Kankate ·
Bhavinkumar N. Chaudhari ·
Rohini D. Kakad

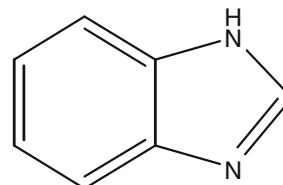
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Abstract Benzimidazole is an interesting heterocyclic compound because it is found in various drugs such as bifeprunox, pimozone, droperidol, etc. The efficacy of substituted benzimidazoles in the treatment of psychoses is well known. Substituted benzimidazole moieties are established pharmacophores in schizophrenia chemotherapy. Benzimidazole derivatives have proven to be of great potential in determining a wide range of activity by binding to various receptors. In addition, piperazinyl moieties linked to benzimidazole enhances the activity at the DA receptors to a greater extent. Various routes have been adopted for the synthesis of derivatives having comparable anti-psychotic activity at various receptors. Dopamine receptors have the potential to mediate activity to varying extent through the binding of ligands, upon it. In this review, binding affinity values of various substituted parent compounds to various dopamine receptors as well as few 5-HT receptors with antipsychotic activity have been tabulated and the synthetic scheme of the same has been shown. This review is summarized to know about various benzimidazolo-piperazinyl ligands that have potential to bind at the dopamine receptors.

Keywords Antipsychotic activity · Benzimidazole · Dopamine receptors · Ligands · Piperazine

Introduction

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole rings. At present, it is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B₁₂ (Barker *et al.*, 1960; Walia *et al.*, 2011).



1H - benzimidazole
(Barker HA *et al.*, 1960)

Piperazines are another class of organic heterocyclic compounds that consists of a six-membered ring containing two nitrogen atoms. The piperazines are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine functional group (Merck Index, 1989; Ashford's Dictionary of Industrial Chemicals, 2011; Chisholm, 1911).

Dopamine is a predominant catecholamine neurotransmitter in the brain, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake and endocrine regulation. This catecholamine also plays multiple roles in

Z. J. Jain (✉) · R. S. Kankate · B. N. Chaudhari · R. D. Kakad
Department of Pharmaceutical Chemistry, M.E.T's Institute of
Pharmacy, Pune University, Nashik, Maharashtra 422003, India
e-mail: zenishjain@gmail.com

the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion vascular tone, renal function, and gastrointestinal motility. Dopaminergic systems have been the focus of research since past 30 years mainly because several pathological conditions, such as Parkinson's disease, schizophrenia, Tourette syndrome, hyperprolactinemia, substance addiction, affective disorders, and attention-deficit hyperactivity disorders, have been linked to dysregulation of dopaminergic transmission.

Dopamine receptor antagonists have been developed to block hallucinations and delusions that occur in schizophrenia patients, whereas dopamine receptor agonists are effective in alleviating the hypokinesia of Parkinson's disease. However, desensitization of DA receptors can induce extrapyramidal effects resulting from DA depletion, and high doses of agonists can cause psychoses. The therapies of disorder resulting from dopamine imbalances are thus associated with several side effects. The complementary DNAs of the five distinct DA receptor subtypes (D1–D5) have been in fact isolated and characterized by application of gene-cloning procedure. A classical requirement to elucidate the functional role of individual receptor subtypes is identification of selective agonists and antagonists (Missale *et al.*, 1998).

Wide range of antipsychotic drugs have been synthesized until today which have shown their varying affinity toward D1, D2, D3, D4, 5-HT_{1A}, and 5-HT_{2A} receptors. Drugs may or may not have affinity toward all the above receptors, but they have higher selectivity toward a specific receptor where they act as agonist or antagonist. This in turn depends on the nature of the parent molecule and the type of substituent attached to the parent moiety. Dopamine receptor antagonism plays a key role in mediation of antipsychotic effect. Novel antipsychotic derivatives have been synthesized to act at a specific receptor and exert their action against various indications of psychoses, i.e., schizophrenia, persistent delusional disorders, chronic hallucinatory psychoses, bipolar disorder, personality disorder, schizoaffective disorders, and Schizotypy disorders (Kebabian and Calne, 1979; Missale *et al.*, 1998). The review will start with a general study on structure of dopamine receptors. The detailed account of the structures of various benzimidazole piperazinyl compounds and their interaction with enzymes has been summarized. Finally, the synthetic scheme of each compound along with chemistry has been discussed.

Structure of dopamine receptors

Analysis of the primary structure of the cloned DA receptors revealed that they are members of the seven

transmembrane (TM) domain G protein-coupled receptor family and share most of their structural characteristics (Fig. 1). Members of this family display considerable amino acid sequence conservation within TM domains (Probst *et al.*, 1992).

Analysis of DA receptor structure pointed to similarities and dissimilarities between D1-like and D2-like receptors (Civelli *et al.*, 1993; Gingrich and Caron, 1993; Jackson and Westlind-Danielsson, 1994; O'Dowd, 1993). Members of the same family share considerable homology. The D1 and D5 receptors share an 80 % identity in their TM domains. The D2 and D3 receptors have a 75 % identity in their TM domains, and the D2 and D4 receptors share a 53 % identity in the TM domains. Fig. 1 shows structural features of the D1-like receptors, whereas the D2-like receptors are characterized by a shorter COOH-terminal tail and by a bigger third intracellular loop (Missale *et al.*, 1998).

The NH₂-terminal stretch has a similar number of amino acids in all the receptor subtypes and carries a variable number of consensus *N*-glycosylation sites. The D1 and D5 receptors possess two such sites, one in the NH₂ terminal and the other one in the second extracellular loop. The D2 receptor has four potential glycosylation sites, the D3 has three, and the D4 possesses only one (Civelli *et al.*, 1993; Gingrich and Caron, 1993; Jackson and Westlind-Danielsson, 1994; O'Dowd, 1993).

The COOH terminal is about seven times longer for D1-like receptors than for the D2-like receptors (Fig. 1).

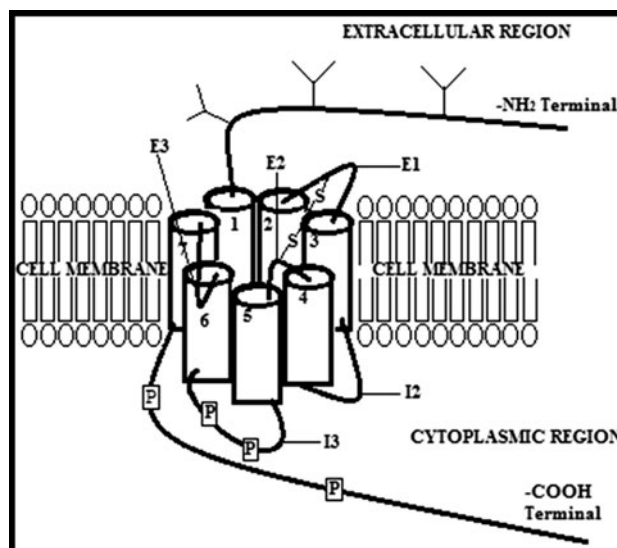


Fig. 1 Representation of a general dopamine receptor structure (D1-like). The active phosphorylation sites are represented on the –COOH terminal and the third intracellular loop (I3) whereas the active glycosylation sites are represented on –NH₂ terminal (Strange 1996). E1–E3:extracellular loops, I2–I3:intracellular loops, 1–7:transmembrane domains

Likewise, as in all G protein-coupled receptors, DA receptors possess two cysteine residues in extracellular loops 2 and 3 (Civelli *et al.*, 1993; Gingrich and Caron, 1993; Jackson and Westlind-Danielsson, 1994; O'Dowd, 1993), which have been suggested to form an intramolecular disulfide bridge to stabilize the receptor structure (Dohlman *et al.*, 1990; Fraser, 1989). The D2-like receptors have a long third intracellular loop, a feature which is common to receptors interacting with inhibitory, Gi proteins to inhibit AC, whereas the D1-like receptors are characterized by a short third loop as in many receptors coupled to stimulatory, Gs protein (Civelli *et al.*, 1993; Gingrich and Caron, 1993; O'Dowd, 1993).

The D1 and D5 receptor's third intracellular loop and their –COOH terminus are similar in size but divergent in their sequence. In contrast, the small cytoplasmic loops 1 and 2 are highly conserved so that any difference in the biology of these receptors can be probably related to the third cytoplasmic loop and the –COOH terminal tail (Civelli *et al.*, 1993; Gingrich and Caron, 1993; O'Dowd, 1993). The external loop between TM4 and TM5 is considerably different in the two receptor subtypes, being shorter (27 amino acids) in the D1 receptor than in the D5 receptor (41 amino acids). The amino acid sequence of this loop, in addition, is divergent in the D5 and in its rat counterpart D1b (Sunahara *et al.*, 1991; Tiberi *et al.*, 2004).

Site-directed mutagenesis for catecholamine receptors (Kjelsberg *et al.*, 1992; Strader *et al.*, 1989; Strader *et al.*, 1988) and protein modeling with the β_2 -, α_2 -, and D2 receptors (Hibert *et al.*, 1992; Hibert *et al.*, 1993; Trumpp-Kallmeyer *et al.*, 1992) suggested that the agonist binding likely occurs within the hydrophobic TM domains (Fig. 1). Highly conserved residues are present in the core of the protein and define a narrow binding pocket that most probably corresponds to the agonist binding site (Hibert *et al.*, 1993). In particular, an aspartate residue in TM3 is most probably involved in binding the amino group of the catecholamine side chain (Strader *et al.*, 1988; Hibert *et al.*, 1993). Two serine residues in TM5 have been shown to be hydrogen bond donors to bind the hydroxyl groups of the catechol moiety for the β_2 - (Strader *et al.*, 1989), α_2 - (Wang *et al.*, 1991), D2 (Cox *et al.*, 1992; Mansour *et al.*, 1992), and D1 (Tomic *et al.*, 2004) receptors. A phenylalanine in TM6 is highly conserved in all receptors interacting with catecholamine neurotransmitters and can make a stabilizing orthogonal interaction with the aromatic moiety of the ligand. A highly conserved aspartate residue in TM2 has been shown to play a crucial role in β_2 -adrenergic (Strader *et al.*, 1988; Hibert *et al.*, 1993; Chung *et al.*, 1988), α_2 -adrenergic (Wang *et al.*, 1991), and D1 (Tomic *et al.*, 1993) and D2 dopaminergic (Neve *et al.*, 1991) receptor activation and to affect agonist binding (Hibert

et al., 1993; Tomic *et al.*, 2004; Sidhu *et al.*, 1992). It has been suggested that the interaction between this aspartate and the agonist is allosteric and can be modulated by Na/or H/ (Hibert *et al.*, 1992; Horstman *et al.*, 1990; O'Dowd *et al.*, 1989). A number of cytoplasmic residues, such as the DRY sequence in the second intracellular loop or the alanine residue in the third intracellular loop of the α -adrenoceptor, also play a role in receptor activation (Kjelsberg *et al.*, 1992; Strader *et al.*, 1988).

Benzimidazole piperazinyl (arylpiperazines) affinity

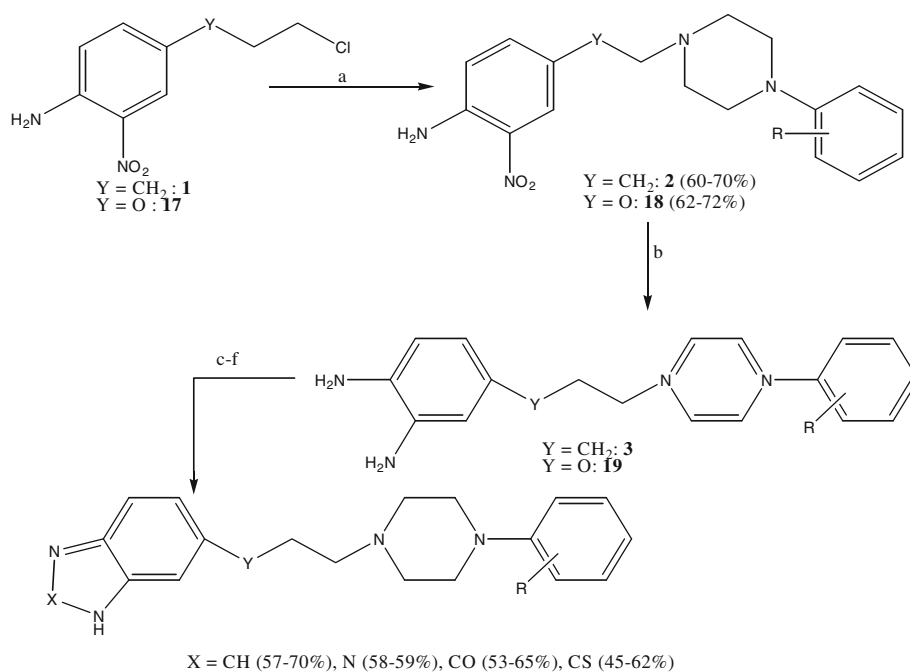
Example 1

Within the scope of the program aimed at the discovery of new dopaminergic ligands, a series of benzimidazoles were synthesized (Soskic and Joksimovic, 1998). The most active compounds were obtained by connecting benzimidazole ring through a flexible spacer with *N*-arylpiperazines, structure of one such example that produces ligand in such a way is presented in Chart 1. It was observed that the affinity of the obtained ligands for the binding to the D2 dopamine receptor depends on both the structure of benzimidazole and arylpiperazine part of the molecule and the spacer itself (Roglic *et al.*, a, b). In order to obtain a better structure-dopaminergic activity relationship and to evaluate the influence of the spacer in this type of ligands on their binding affinity, various benzimidazolopiperazinyl derivatives have been synthesized, evaluated, and docking analyses of a series of new compounds has been performed (Klocker *et al.*, 2003a, b); therefore, ligand–receptor interaction can be effected on several levels.

Chemistry (Scheme 1)

The derivatives **1–13** and **20–43** (Table 1) were synthesized as outlined in Scheme 1. Compounds with propylene spacer were prepared according to previously described strategy (Roglic *et al.*, 2001a) starting from 4-(3-chloropropyl)-2-nitroaniline (**1**). Ethylenoxy compounds were obtained starting from 4-(2-chloroethoxy)-2-nitroaniline (**17**) as a parent compound (Sukalovic *et al.*, 2005). Briefly, 1-(2-chloroethoxy)-4-nitrobenzene (**14**) was prepared by alkylating 4-nitrophenol with 1, 2-dichloroethane. A simultaneous reduction and acetylation with zinc dust in acetanhydride/acetic acid mixture afforded acetanilide (**15**). Nitration of **15** in boiling 20 % nitric acid gave *o*-nitroacetanilide (**16**) that was further hydrolyzed to *o*-aniline **17** with boiling HCl. Compound **17** readily alkylates *N*-phenyl-piperazine in DMF in the presence of K₂CO₃ and K_i at elevated temperature affording 2-nitro-4-[2-(4-

Scheme 1 Synthesis of 5-[3-(4-arylpiperazine-1-yl)propyl]-1*H*-benzimidazole, 5-[2-(4-arylpiperazine-1-yl)ethoxy]-1*H*-benzimidazole and their analogs. **a** Arylpiperazine, K_2CO_3 , DMF. **b** Ra–Ni, N_2H_4 , EtOH, DCE. **c** $HCOOH$, reflux. **d** CS_2 , KOH, EtOH. **e** 1,1'-carbonyldiimidazole and **f** $NaNO_2$, AcOH. Obtained yields are claimed in parentheses



arylpiperazin-1-yl)ethoxy]-anilines (**18**). Further reduction with Ra–Ni/hydrazine afforded *o*-phenylenediamines **19**. Target benzimidazoles (**4–8** and **20–24**), benzimidazole-2-thiones (**9–13** and **25–32**), benzimidazole-2-ones (**33–40**) and benzotriazoles (**41–43**) were prepared as described earlier (Soskic and Joksimovic, 1998).

Example 2: selective dopamine D3 ligands-II

Compound B had high affinity for DA D3 receptors ($K_i = 1.5$ nM) with much weaker affinity for D2 receptors ($K_i = 406$ nM) (Svensson *et al.*, 1994). Thus, arylpiperazine analogs of compound **3** were prepared to explore the potency and selectivity of this novel lead for DA D3 receptors (Svensson *et al.*, 2003).

Chemistry (Scheme 2)

The synthesis of compound **3** and analogs is shown in Scheme 2 (Wright *et al.*, 1994) Step (i) could be performed with 2 equivalents of the piperazine instead of using triethylamine to neutralize the HBr formed. However, the piperazines were often in short supply and the use of triethylamine allowed all of the piperazine to be converted to product.

The importance of the phenylpiperazine group for DA D3 binding potency was examined via preparation and testing of the analogs shown in Table 2. Replacement of phenylpiperazine with methylpiperazine (compound **1**)

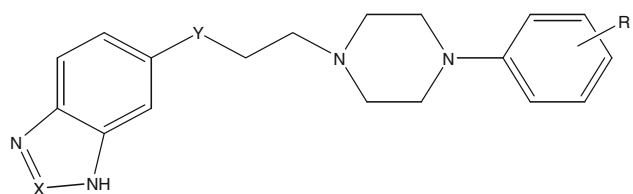
greatly reduces DA binding. This result clearly separates the SAR of this series from that of the previously described dimeric series. In that series, dialkylamines were the most active; phenylpiperazine was inactive. As the phenyl was important for DA D3 binding, a Topliss analysis of substituents on the phenyl ring was undertaken (the aryl piperazine starting materials are all known).

The 4-chlorophenyl analog **2** had weaker DA binding affinity than the phenyl parent B. The Topliss analysis thus suggested that 4-methoxyphenyl analog **3** although had weaker DA D3 binding, but improved D2 binding. In this case, the Topliss analysis proposed the 3-chlorophenyl analog **4**. This compound also had weaker affinity for DA D3 receptors. The Topliss analysis, along with several other analogs not reported here concluded that aromatic substitution on the phenylpiperazine group of B will not enhance DA D3 binding.

An unexpected result was seen with 2-substituted phenyl compounds **5–7**. These had high affinity for DA D3 receptors, but were disappointingly non-selective due to strong binding to D2 receptors. The 2-pyridylpiperazine and 2-pyrimidylpiperazine analogs **8** and **9** were both reasonably potent at DA D3 receptors but were again less interesting due to moderate affinity for D2 receptors.

From this study, compound **3** showed optimal affinity and selectivity for DA D3 receptors and was evaluated further.

Table 1 Chemical structure and binding affinity (K_i) of the examined benzimidazole piperazines and other arylpiperazine ligands for the D₁ and D₂ dopamine receptors (Sukalovic *et al.*, 2005):



(A)

| Compound no. | X | Y | R | * K_i (nM) \pm SEM | |
|--------------|-----|-----------------|-------------------|------------------------|-----------------|
| | | | | D1 | D2 |
| 4 | CH | CH ₂ | H | >1,000 | 129 \pm 19 |
| 5 | CH | CH ₂ | 3-CF ₃ | >1,000 | >1,000 |
| 6 | CH | CH ₂ | 4-Cl | >1,000 | >1,000 |
| 7 | CH | CH ₂ | 4-OMe | >1,000 | >1,000 |
| 8 | CH | CH ₂ | 2-OMe | >1,000 | 97 \pm 21 |
| 9 | C=S | CH ₂ | H | >1,000 | 3.0 \pm 0.2 |
| 10 | C=S | CH ₂ | 3-CF ₃ | >1,000 | 5.8 \pm 0.4 |
| 11 | C=S | CH ₂ | 4-Cl | >1,000 | 20 \pm 2.8 |
| 12 | C=S | CH ₂ | 4-OMe | >1,000 | 33 \pm 4.2 |
| 13 | C=S | CH ₂ | 2-OMe | >1,000 | 0.4 \pm 0.05 |
| 20 | CH | CH ₂ | H | >1,000 | 274 \pm 18 |
| 21 | CH | O | 3-CF ₃ | >1,000 | >1,000 |
| 22 | CH | O | 2-MeO | >1,000 | 12.6 \pm 0.9 |
| 23 | CH | O | 3-MeO | >1,000 | >1,000 |
| 24 | CH | O | 4-MeO | >1,000 | >1,000 |
| 25 | C=S | O | H | >1,000 | 0.67 \pm 0.06 |
| 26 | C=S | O | 3-CF ₃ | >1,000 | 5.94 \pm 0.3 |
| 27 | C=S | O | 2-MeO | >1,000 | 0.19 \pm 0.06 |
| 28 | C=S | O | 3-MeO | >1,000 | 13.2 \pm 1.2 |
| 29 | C=S | O | 4-MeO | >1,000 | 105 \pm 8.1 |
| 30 | C=S | O | 2-Cl | 446 \pm 32 | 2.75 \pm 0.4 |
| 31 | C=S | O | 3-Cl | >1,000 | 7.06 \pm 0.9 |
| 32 | C=S | O | 4-Cl | >1,000 | >1,000 |
| 33 | C=O | O | H | >1,000 | 7.53 \pm 1.0 |
| 34 | C=O | O | 3-CF ₃ | >1,000 | 26.1 \pm 4.2 |
| 35 | C=O | O | 2-MeO | >1,000 | 1.30 \pm 0.1 |
| 36 | C=O | O | 3-MeO | >1,000 | 44.8 \pm 6.2 |
| 37 | C=O | O | 4-MeO | >1,000 | >1,000 |
| 38 | C=O | O | 2-Cl | 405 \pm 30 | >1,000 |
| 39 | C=O | O | 3-Cl | >1,000 | 45.5 \pm 3.0 |
| 40 | C=O | O | 4-Cl | >1,000 | >1,000 |
| 41 | N | O | H | >1,000 | >1,000 |
| 42 | N | O | 3-CF ₃ | >1,000 | >1,000 |
| 43 | N | O | 2-MeO | >1,000 | 1.51 \pm 0.4 |

Structure of 5-[3-(4-arylpiperazine-1-yl)propyl]-1H-benzimidazoles and 5-[2-(4-arylpiperazine-1-yl)ethoxy]-1H-benzimidazoles and their analogs tested for the binding to the D₁ and D₂ dopamine and 5-HT_{1A} serotonin receptors is shown. K_i values are the means of three independent experiments done in triplicate performed at eight to 10 competing ligand concentrations

* K_i binding affinity in nM (nanomoles), SEM standard error of the mean

Example 3

During the last decade, the strategy focused on drug design and synthesis of mixed dopaminergic–serotonergic compounds was followed with a possible atypical neuroleptic potential. One of the synthetic approaches was the design and synthesis of heterocyclic arylpiperazines with a specific structure of heteroaryl group that mimics catechol moiety of the dopamine (benzimidazole, substituted benzimidazoles, benzotriazoles, and 1,4-dihydroquinoxaline-2,3-diones). Variations of heterocyclic and aryl groups had produced over 100 new compounds that were screened for their affinities at bovine brain D₁, D₂, and 5-HT_{1A} receptors by in vitro radioligand binding assays (Dukic *et al.*, 1997a, b; Kostic-Rajacic *et al.*, 1998) The six most active compounds (Table 3) were selected for further pharmacological examinations.

All compounds expressed a higher affinity for the 5-HT_{1A} receptors comparing to clozapine for up to one order of magnitude (Table 3). Only two compounds (**2** and **3**) showed a higher affinity for 5-HT_{2A} than D₂ receptors, and this was more prominent for compound **2** (K_i of 5.10 and 51.3 nM at 5-HT_{2A} and D₂ receptors, respectively). Compound **2** expressed a comparable affinity to clozapine for the D₂, 5-HT_{2A}, and α_1 -adrenergic receptors, and somewhat lower affinity for the 5-HT_{2C} receptors. It exhibited a poor affinity at the D₁ receptor and no binding potency at the 5-HT₃ receptor. On the other hand, compound **2** showed a higher affinity for the 5-HT_{1A} receptor than clozapine (K_i values of 90.2 and 415 nM, respectively) and a certain potential to inhibit in vitro synaptosomal 5-HT uptake (IC_{50} = 260 nM). However, the inhibitory strength of compound **2** for 5-HT reuptake, although higher than that of compounds **1** and **3**, seems to be fairly low to take into account its possible antidepressive ability by this mechanism, proposed for some new atypical APDs (Meltzer *et al.*, 2003).

Example 4: chemistry

Drug design strategies toward novel dopamine D₂ agonists have been based predominately around the endogenous neurotransmitter dopamine (DA, compound **1**). (Kaiser and Jain, 1985; Seyfried and Boettcher, 1990; Wikstrom, 1992). Traditional dopamine agonists have a close resemblance to DA (**1**), most having the ‘3-OH-phenethylamine’ DA pharmacophore (**2**) or a bioisosteric surrogate, embedded within their molecular structure, e.g., compound **3** (Wikstrom *et al.*, 1989). Studies from various laboratories have resulted in the emergence of a new generation of dopaminergic agents that no longer rely upon

Scheme 2 *i* Et₃N, CH₂Cl₂, reflux, 2 h. *ii* NaH, DMF, 60 °C, 12 h. *iii* 1,2-diaminobenzene, NaHSO₃, MeOH, reflux, 4 h

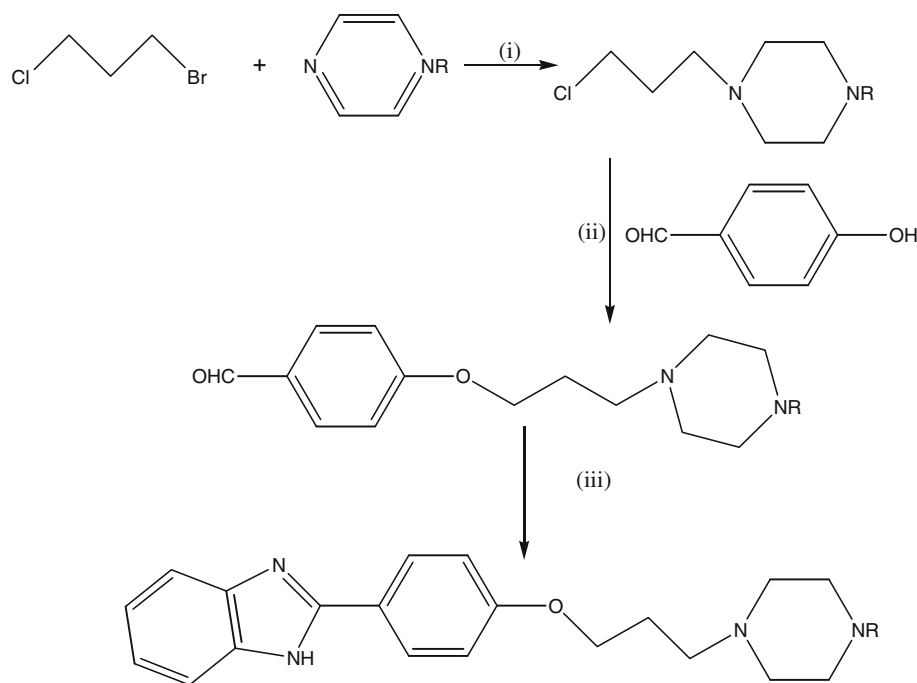
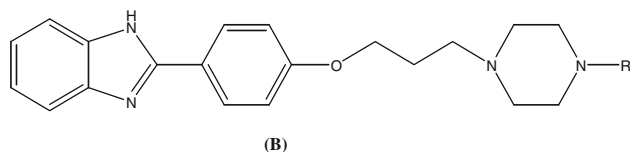


Table 2 DA receptor binding for compound B and its analogs (Wright *et al.*, 1995)



| Compound | R | D3 Binding K_i (nM) | D2 Binding K_i (nM) |
|----------|-------------|--------------------------|--------------------------|
| B | Ph | 1.5 | 406 |
| 1 | Me | 2,000 | >3,333 |
| 2 | 4-ClPh | 27 | 865 |
| 3 | 4-MeOPh | 130 | 293 |
| 4 | 3-ClPh | 155 | 1,403 |
| 5 | 2-ClPh | 18 | 126 |
| 6 | 2-PrSPh | 1.3 | 8 |
| 7 | 2-MeOPh | 1.7 | 8.8 |
| 8 | 2-Pyridyl | 8 | 70 |
| 9 | 2-Pyrimidyl | 15 | 269 |

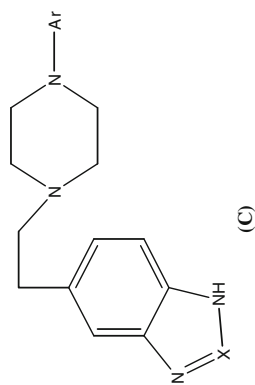
the ‘3-OH-phenethylamine’ framework (Mewshaw *et al.*, 1998a, b, c).

In the Scheme 3, the synthesis and structure–activity relationships of various indole, indolone, benzimidazolone, and benzimidazole derivatives (i.e., **5–7** and **9–13**) based on the 3-OH-N¹-phenylpiperazine DA D2 template (4) is disclosed. The initial efforts resulted in the identification of

several phenolic D2 agonist prototypes (e.g., **4**) (Mewshaw *et al.*, 1998a, b, c) that can be used as templates for the design of bioisosteric analogs. As part of a program to discover compounds that could be potentially useful as antipsychotic drugs, embarkment on exploiting these phenolic prototypes by preparing several heterocyclic bioisosteric analogs is done.

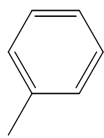
Shown in Tables 4 and 5 are the affinities of the target compounds (i.e., **5–7** and **9–13**) for the D2-like receptors. The affinities of compounds for the D2 receptors in rat striatal membranes were determined for both the agonist state (high affinity state, D2^{High}) and the antagonist state (low affinity state, D2^{Low}). The D2^{High} state was labeled with [³H] quinpirole (in the absence of GTP and sodium) and the D2^{Low} state was labeled with [³H] spiperone (using ketanserin to exclude 5-HT₂ receptor binding) in the presence of GTP. The ratio K_i (D2^{Low})/ K_i (D2^{High}) was used as a preliminary and reliable estimate of the compounds’ intrinsic activity as determined by other assays (Lahti *et al.*, 1992; Wasik *et al.*, 1996). The D2 partial agonist (S)-3-PPP [K_i (D2^{Low})/ K_i (D2^{High}) = 33], was used as a benchmark from which a compound’s estimated intrinsic activity was compared. Affinity for the human cloned receptors was determined using membranes from CHO cells labeled with [³H] spiperone.

As shown in Table 4, replacement with the phenol moiety of 4 with the indolone bioisostere (i.e., compound **5**) resulted in a tenfold increase in affinity for the D2^{High} receptor and a similar predicted intrinsic activity ratio [K_i (D2^{Low})/ K_i (D2^{High}) = 14]. Indolone **5** was observed to have high affinity for all the D2-like receptors and was one

Table 3 DA receptor binding affinity and inhibition of 5-HT uptake for compounds **1–6** and clozapine (84)

| Compound ^A | X | Ar | p <i>K</i> _i ± S.E.M. | | | IC ₅₀ (μM) ± SEM-5-HT uptake | | | | | 5-HT _{2A} /D ₂ binding ratio | |
|-----------------------|-------|----|----------------------------------|----------------|--------------------|---|--------------------|-------------------|--------------------|--------------------|--|-------------------|
| | | | D ₁ | D ₂ | 5-HT _{1A} | 5-HT _{2A} | 5-HT _{2C} | 5-HT ₃ | 5-HT _{2A} | 5-HT _{2C} | | 5-HT ₃ |
| 1 | CH | | 5.4 ± 0.1 | 8.78 ± 0.02 | 6.90 ± 0.09 | 7.82 ± 0.15 | 7.19 ± 0.11 | 5.28 ± 0.11 | 1.76 ± 0.52 | | | 0.89 |
| 2 | N | | 5.33 ± 0.11 | 7.29 ± 0.06 | 7.08 ± 0.05 | 8.29 ± 0.14 | 7.84 ± 0.08 | <5 | 0.26 ± 0.07 | | | 1.14 |
| 3 | N | | 5.24 ± 0.12 | 7.62 ± 0.18 | 7.41 ± 0.16 | 7.98 ± 0.12 | 7.26 ± 0.13 | <5 | > 10 | | | 1.05 |
| 4 | N | | 6.09 ± 0.09 | 8.27 ± 0.14 | 7.10 ± 0.11 | 6.85 ± 0.12 | 7.35 ± 0.02 | <5 | – | | | 0.83 |
| 5 | CO-CO | | – | 7.55 ± 0.20 | 7.06 ± 0.16 | 5.81 ± 0.10 | – | – | – | | | 0.77 |

Table 3 continued

| Compound ^a | X | Ar | pK _i ± S.E.M. | | IC ₅₀ (μM) ± SEM-5-HT uptake | | | | | | 5-HT _{2A} /D ₂ binding ratio |
|-----------------------|---------------------------------|---|--------------------------|----------------|---|--------------------|--------------------|-------------------|--------------------|-------------------|--|
| | | | D ₁ | D ₂ | 5-HT _{1A} | 5-HT _{2A} | 5-HT _{2C} | 5-HT ₃ | 5-HT _{2C} | 5-HT ₃ | |
| 6 | C-C ₆ H ₅ |  | – | 7.5 ± 0.05 | 6.76 ± 0.13 | 6.12 ± 0.11 | – | – | – | – | 0.82 |
| Clozapine | | | 7.5 ± 0.14 | 7.11 ± 0.05 | 6.38 ± 0.1 | 8.57 ± 0.18 | 8.54 ± 0.02 | 6.73 ± 0.19 | >10 | | 1.02 |

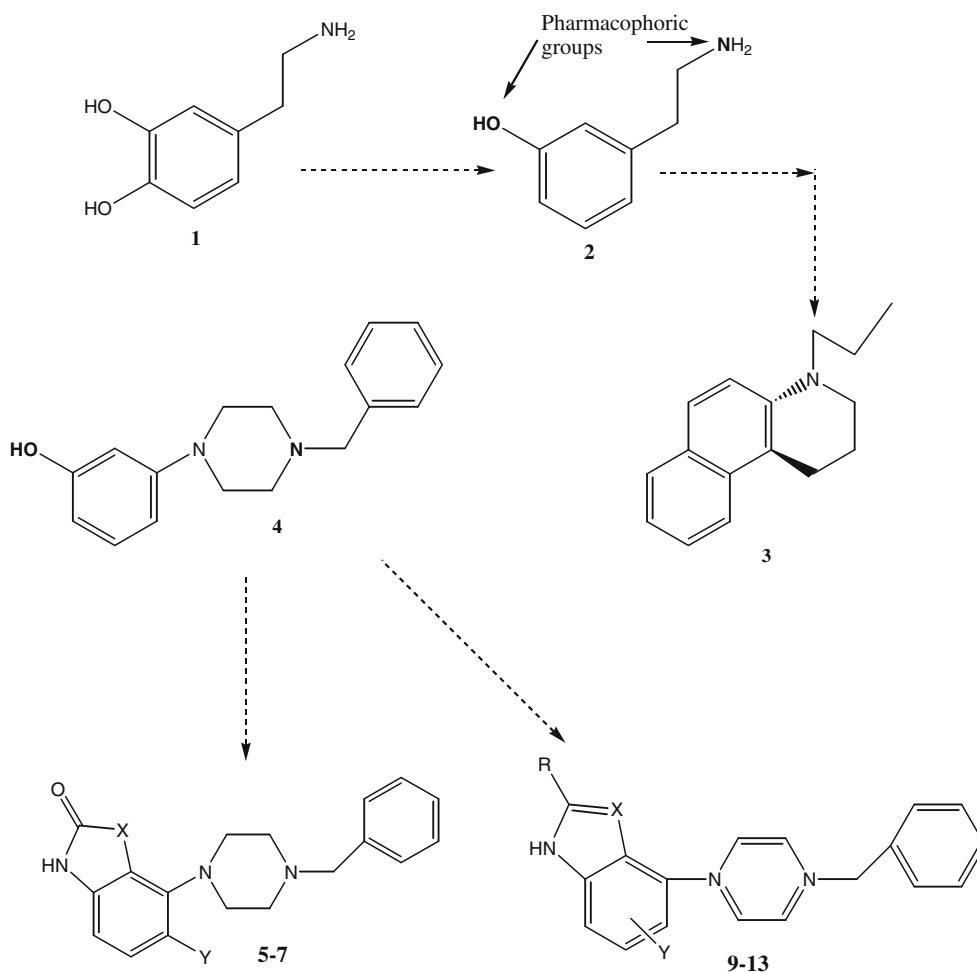
^a Details on complete synthesis and structural analysis of all six compounds are described by Dukic *et al.*, 1997a; Kostic-Rajacic *et al.*, 1998

of the most potent compounds identified in this study. Though the 5-chloro derivative (**6**) had unimpressive affinity for the D₂^{High} receptor, it was observed to exhibit selectivity for the hD_{4.4} receptor. Benzimidazolone **7** had similar affinity to its phenol analog (**4**) with a slight preference for the hD_{4.4} receptor. Indole, **9** (Table 4) was found to have similar D₂^{High} affinity as its phenol prototype (i.e., compound **4**); however, a lower predicted intrinsic activity than **4** was observed [**9**; ($K_i(D_2^{Low})/K_i(D_2^{High}) = 5$)]. Introduction of either a bromine or chlorine into compound **9** (i.e., **10** and **11**) resulted in compounds having selectivity for the hD_{4.4} receptor. Though benzimidazole **12** had good affinity for the D2-High receptor, introduction of the trifluoromethyl group led to a 19-fold increase in D2-High affinity. In fact, the benzimidazole (**13**) had similar affinity as its indolone analog (**5**) for the D2-High receptor, revealing that the indolone and 2-CF₃-benzimidazole groups can both serve as surrogate phenol bioisosteres.

Consistent with the predicted low intrinsic activity, *in vivo* studies showed both **5** and **13** to reduce spontaneous locomotor activity (ED₅₀ = 0.12 mg/kg sc for **13**; **5** decreased activity at 0.01, 0.03, 1, and 3 mg/kg sc) and to inhibit apomorphine-induced stereotypy (S) and climbing (C) in mice (ED₅₀s for **13**: S = 13.8 mg/kg sc, C = 0.4 mg/kg sc; for **5**: S = 1.5 mg/kg sc, C = 2.3 mg/kg sc). Unlike **5**, benzimidazole **13** induced catalepsy at 10 mg/kg sc in mice, which correlates with their predicted intrinsic activity ratios (**6** vs **14**).

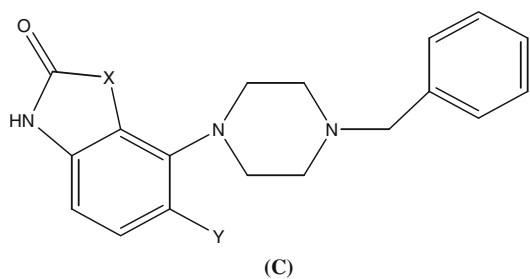
Conclusion

It is concluded that among the aryl piperazines, benzimidazolo-piperazines together are effective in binding to the dopamine receptors as well as 5-HT receptors. By varying the substitutions on benzimidazolo-piperazinyl moiety, the compound affinity and preference to various dopamine receptor subtypes are altered and thereby their binding constants are altered. For suitable binding, there is a requirement of a suitable distance between hydroxyl (if present) and a distant nitrogen atom which can be studied through docking analysis. Also, benzimidazolones (indoles and indolones) piperazinyl class of derivatives has been found to possess varying D2 and D4 affinity. Also, the long alkoxy chain separating the benzimidazole and piperazine has given derivatives with increased D3 receptor affinity. There is a wide scope for the synthetic scientists to synthesize more and more compounds with different substitutions using benzimidazole and piperazine as a basic moiety. Thus, investigation and probing of the boundaries of the D2 agonist pharmacophoric criteria is being continued by identifying potential antipsychotic agents that belong to this new generation of dopaminergic agents



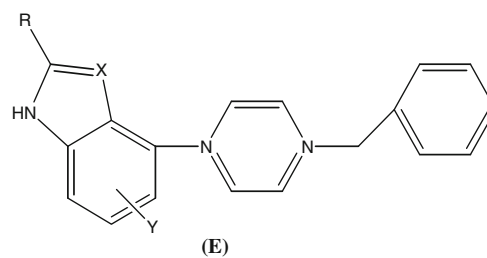
Scheme 3 Synthesis and structure-activity relationships of various analogs based on the 3-OH-N¹-phenylpiperazine moiety

Table 4 Affinity of indolones (5 and 6) and benzimidazolone (7) for D2–D4 receptors



| K_i (nM) ¹² | | | | | | | | |
|--------------------------|-----------------|----|--------------------|-------------------|---------------------------------------|------------------|-----------------|-------------------|
| No | X | Y | D2 ^{High} | D2 ^{Low} | D2 ^{High} /D2 ^{Low} | hD _{2s} | hD ₃ | hD _{4.4} |
| 4 ⁶ | | | 5.5 | 95.1 | 17 | 246 | 28.9 | >400 |
| 5 | CH ₂ | H | 0.56 | 8.1 | 14 | 8 | 5.4 | 3 |
| 6 | CH ₂ | Cl | 54.8 | 403 | 7 | 540 | 591.3 | 8.8 |
| 7 | NH | H | 4.2 | 45.8 | 11 | 87.3 | 56.5 | 14.4 |

Table 5 Affinities of indoles (9–11) and benzimidazoles (12 and 13) and for D2–D4 receptors



| K_i (nM) ¹² | | | | | | | | | |
|--------------------------|----|----|-----------------|--------------------|-------------------|---------------------------------------|------------------|-----------------|-------------------|
| No | X | Y | R | D2 ^{High} | D2 ^{Low} | D2 ^{High} /D2 ^{Low} | hD _{2s} | hD ₃ | hD _{4.4} |
| 9 | CH | H | H | 3.2 | 17.4 | 5 | 53 | 35.4 | 14.7 |
| 10 | CH | 7- | H | 26.8 | 12.2 | 0.5 | 47 | 56 | 2.6 |
| | | Br | | | | | | | |
| 11 | CH | 5- | H | 9.1 | 42.3 | 5 | 81.3 | 95.3 | 1.7 |
| | | Cl | | | | | | | |
| 12 | N | H | H | 9.7 | 107 | 11 | 257.5 | 870.5 | 47 |
| 13 | N | H | CF ₃ | 0.51 | 3.3 | 6 | 4.1 | 14.7 | 2.9 |

which in turn could possess optimum antipsychotic activity.

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