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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of 3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole analogues and their evaluation as anti-Parkinson′s agents

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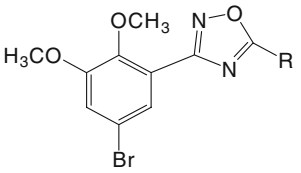
Abstract A series of 3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole derivatives was prepared and their evaluation for anti-Parkinson's activity was measured in vivo using albino rats. The result of the biological activity studies indicated that some of the synthesized compounds have good agonistic activity on the dopamine receptors and a few of them were also found to be free from neurotoxicity. Thus these compounds might be useful ligands for studying the functional role of dopamine receptors in vivo. The high log *P* value of the compounds indicates that they should easily cross the blood-brain barrier (log $P > 2.6$).



Keywords Dopamine receptor antagonist · Antiparkinson · Oxadiazole

Introduction

Parkinson's disease (PD) and Alzheimer disease (AD) are the most common neurodegenerative disorders. They affect at least 5% of the population above the age of 65 years (McDowell, 2001). The current drug therapy used for PD consists mainly of L-dopa and/or dopamine (DA) agonist, monoamine oxidase B inhibitors such as rasagiline, selegline, catechol-*O*-methyl transferase inhibitor (COMT), and

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entacapone. These drugs can improve clinical symptoms but cannot mitigate progression of the disease process underlying PD (Mandel *et al*., 2003). Dopamine receptors are G-protein coupled receptors and share a characteristic seven transmembrane domain. The five-dopamine receptor subtypes are classified into two categories (Drukarch and maiswinkel, 2000). The first one is known as the D1 family, containing D_1- and D_5-subtype receptors; they are characterized by activation of adenyl cyclase mediated by G_5 protein consequently effecting higher concentrations of the secondary messenger cyclic adenosine 3,5-monophosphate (cAMP). These receptors lack introns in their coding gene (Levant, 1997). The second category, the D2 family, consists of the D_2, D_3, and D_4 receptors subtypes, which couple to G_1 proteins and can inhibit adenyl cyclase. In the gene of dopamine D2-like receptors introns can be found (Civelli *et al*., 1991; Civelli *et al*., 1993). Within each of dopamine-containing systems dopamine receptors are located either postsynaptically, terminal of afferent fiber projection on the cell bodies, dendrites of neurons or presynaptically on the dopamine nerve terminal (Broughton *et al*., 1975; Waddington, 1993; Hodgetts *et al*., 2001; Cohen *et al*., 1990).

The third intracellular loop exhibits the largest sequence dissimilarities among the different DA receptors. The D_1 and D_5 receptors have relatively short third intracellular loops which are coupled to Gs proteins and have long *C*-terminal tails. These two receptors stimulate the activity of adenyl cyclase and the pharmacological functions of known ligands are more or less identical. The D2-like receptors, i.e., D_2, D_3, and D_4 receptors on the other hand, all have long third intracellular loops with short *C*-terminal tails which might couple to Gi proteins (or G0 proteins) and inhibit adenyl cyclase. Interesting, two forms of the DA D2 receptors have been found, differing in 29 amino acids in the third intracellular loop; they seem to have identical pharmacology but their presence in various cerebral tissues differ. Hence, a difference in functionality is likely still to be found. The long and the short forms of the D2 receptors (D2L and D2S, respectively) consist of 443 and 414 amino acid residues, respectively. The genes of the dopamine receptors superfamily can be divided into two different categories: (1) intronless genes that code for the D1-like receptors and (2) genes with their coding sequences in discontinuous DNA segments (axons) separated by sequences (introns) that do not form a part of the mature mRNA. The latter category of genes are found in the D2-like family of dopamine receptors, which explains the occurrence of a long and a short form of the DA D2 receptor. In the biosynthesis of mRNA a mechanism called alternative splicing, in which a given axon in the pre-mRNA is present or absent in the final mRNA, results in two different proteins coded by the same gene (Fuller *et al*., 1968; John, 2002; Strange, 1993).

Furthermore, both DA neurons and receptors are markedly reduced by normal aging and Parkinson's disease and have been implicated in a variety of other disorders, including schizophrenia and drug abuse. Dopaminergic neurotransmission and dopamine receptors underlie manifold neurological and psychiatric disorders for e.g. Parkinson's disease, Huntington disease, Schizophrenia, Tourette syndrome, Tardive dyskinesia and Drug abuse. (Sedvall and Farade, 1995)

Parkinson's disease is characterized by tremor (uncontrolled shaking), rigidity (muscular rigidity), and akinesia (inability to walk properly). There is no curative treatment for Parkinson's disease till date and the present treatment involves only

eliminating or reducing exposure to the toxic substances followed by symptomatic and supportive therapy (Whitehouse, 1962; Langridge *et al*., 1981; Schoenborn, 1969). This is because there is no drug available for selective dopamine D_2 and D_3 agonism. In view of this and in continuation of our research work towards a cure for Parkinson's disease we synthesized a series of 3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole derivatives. The structural elucidation was carried out by various spectroscopic methods. The compounds were screened for anti-Parkinson's activity as well as neurotoxicity using albino rats in vivo. The result of the biological activity studies indicated that some of the synthesized compounds have good agonistic activity on the dopamine receptors and a few of them were also found to be free from neurotoxicity. Showing an agonistic effect on the dopamine receptors, these synthesized compounds may be very useful for the treatment of Parkinson's disease (Dandiya and Bhargava, 1968).

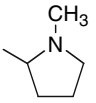
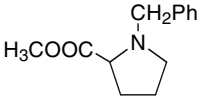
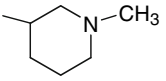
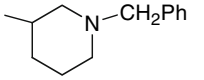
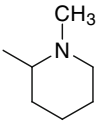
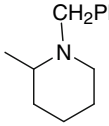
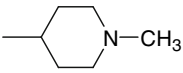
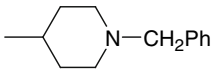
Chemistry

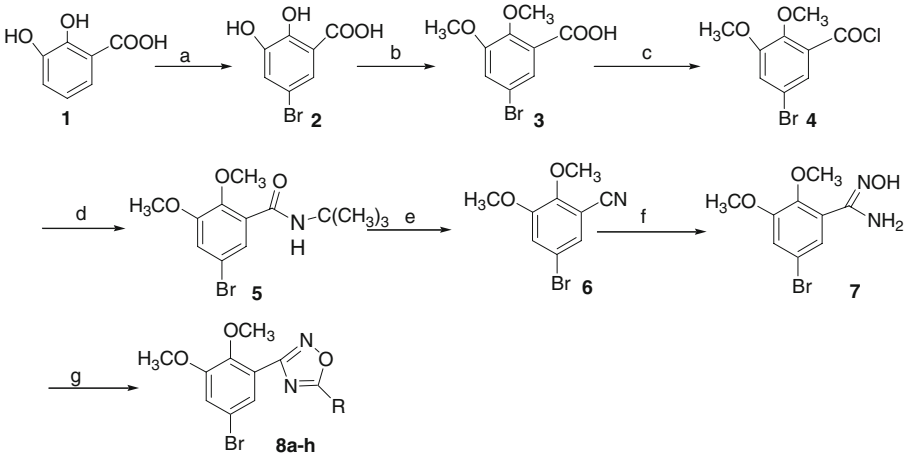
The synthesis of 3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole was accomplished via the sequence reaction outlined in Table 1. 2,3-Dihydroxy benzoic acid (**1**) on bromination afforded 5-bromo-2,3-dihydroxy benzoic acid (**2**), which on methylation gave 5-bromo-2,3-dimethoxy benzoic acid (**3**). 5-Bromo-2,3-dimethoxy benzoic acid (**3**) on reaction with thionyl chloride followed by treatment with tert-butyl amine afforded N-tert-butyl-5-bromo-2,3-dimethoxy-benzamide (**5**). The synthesis of 5-bromo-2,3-dimethoxybenzonitrile (**6**) was accomplished via the treatment of N-tert-butyl-5-bromo-2,3-dimethoxy-benzamide (**5**) with phosphorous oxychloride (Litchfield and Wilcoxan, 1949). The treatment of 5-bromo-2,3-dimethoxybenzonitrile (**6**) with hydroxyl amine in the presence of base afforded 2,3-dimethoxy-5-bromo benzamide oxime (**7**), which on treatment with various alkyl methyl esters gave alkyl 3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole derivatives (**8a-h**).

In Vivo Evaluation

The in vivo performance of the compounds was carried out by assessing the reduction in the degree of drug-induced catatonia (chlorpromazine) in albino rats and compared with dopamine, plain levodopa, and the combination of levodopa and carbidopa. The purpose of this type of study was to demonstrate the anti-Parkinson's activity of the synthesized compounds and its comparison with dopamine, plain levodopa, and the combination of levodopa and carbidopa. The reduction in the degree of drug-induced catatonia (rigidity and akinesia) was assessed by the method described by Kulkarni *et al.* in which the drug is administered intraperitoneally and after 30 min chlorpromazine is administered to induce extrapyramidal effects (tremor, rigidity, and akinesia) (Kulkarni, 1980; Kulkarni *et al*., 1980). (Table 1, Scheme 1).

Table 1 Substituents in the oxadiazole ring

Compound (8a-h)	R	Compound (8a-h)	R
8a		8e	
8b		8f	
8c		8g	
8d		8h	



Scheme 1 (**a**) Br_2, AcOH, rt, 88%; (**b**) $(CH_3)_2SO_4$, acetone, K_2CO_3, reflux, 86%; (**c**) $SOCl_2$, benzene, reflux, 95%; (**d**) t-$BuNH_2$, CH_2CI_2, rt, 96%; (**e**) $POCl_3$, C_6H_6, reflux, 88%; (**f**) $NH_2OH.HCI$, K_2CO_3, EtOH, reflux, 88%; (**g**) NaH, $RCOOCH_3$, HCOOH, alumina, reflux

Seventy-two albino rats were selected, weighed, and divided into 12 groups of six animals each. The animals in the first group were kept as control (without drug administration) while plane dopamine solution (dose 10 mg/kg), plain levodopa

solution (dose 10 mg/kg), and the marketed preparation syndopa (levodopa + carbidopa, dose 2.5 mg/kg), were injected intraperitoneally to the animals in the second, third, and fourth groups respectively. The animals in the fifth to twelve groups were injected with the synthesized compounds **8a-h** intraperitoneally (100 mg/kg). Thirty minutes after administrating the above drugs and synthesized compounds, chlorpromazine (5 mg/kg) was injected intraperitoneally to all the animals to induce catatonia. All the animals were fasted for 12 hours before injection of the drugs. The reduction in the degree of drug-induced catatonia (difficulty to move and change the posture) was assessed by placing the front paw of the rat on a block of 3 and 9 cm height alternatively. The observations are recorded into in Table 2. The comparative responses of drug-induced catatonia are shown in Fig. 1 (time versus mean score of catatonic activity (MSCA) for different molecules). Table 3

Experimental Protocol for Neurotoxicity

Drug interference activity with motor coordination was checked by using the rotorod test (D'Amour and Smith, 1941; Litchfield and Wilcoxan, 1949) in which rats (20–25 g) were trained to stay on a knurled plastic rod (3.2 cm diameter) that was rotated at 10 rpm; normal rats can maintain equilibrium on such a rotating rod for a longer time. The test compounds were injected intraperitoneally at a dose of 200 mg/kg and tested at the time of peak drug effect. The neurotoxicity of compounds was indicated by inability of the animals to maintain equilibrium on the rod for at least 1 min in each of three trials. Rats lost balance due to the skeletal muscle relaxation effect of the drugs. The dose at which 50% of the animals were unable to balance and fell off the rotating rod was determined.

Table 2 Catatonic activity scores in rats

S. no.	Animal group	Compound	MSCA (min)							
			15	30	45	60	90	120	150	180
01	02	Dopamine	0.0	0.84	1.33	2.08	2.667	3.333	3.500	3.500
02	03	Levodopa	0.0	0.68	1.1667	1.9167	2.5833	3.1667	3.500	3.500
03	04	Levodopa + carbidopa	0.0	0.0	0.0	0.0	0.083	0.833	1.167	3.0833
04	05	**8a**	0.0	0.16	0.66	1.00	1.33	1.7	2.83	3.333
05	06	**8b**	0.0	0.25	0.75	1.16	1.5	2.00	3.00	3.417
06	07	**8c**	0.0	0.25	0.75	1.16	1.58	2.08	3.08	3.417
07	08	**8d**	0.0	0.16	0.66	1.08	1.58	1.75	2.92	3.333
08	09	**8e**	0.0	0.083	0.66	1.083	1.42	2.08	3.25	3.333
09	10	**8f**	0.0	0.33	0.75	1.167	1.67	2.33	3.167	3.417
10	11	**8g**	0.0	0.3	0.66	1.08	1.55	2.16	3.167	3.417
11	12	**8h**	0.0	0.08	0.58	0.927	1.334	1.92	2.926	3.333

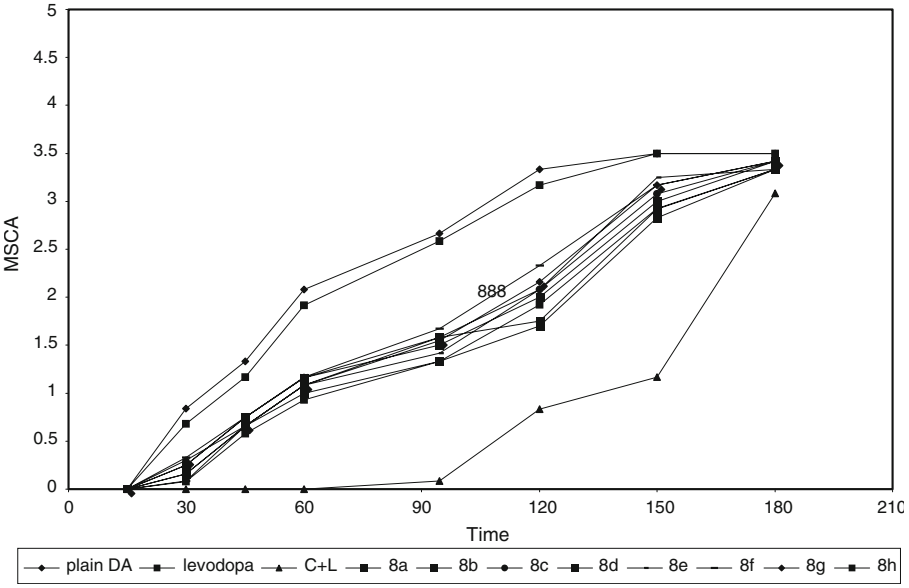


Fig. 1 Comparative response of drug-induced catatonia (time versus MSCA)

Table 3 Mean score of catatonic activity value of the compounds after 180 min, neurotoxicity and log *P* values of the synthesized compounds

S. no.	Compound	Mean Score of Catatonic Activity After 180 Min. (MSCA)	Neurotoxicity testing (30 min)	Log *P*
01	**8a**	3.333	+	3.7901
02	**8b**	3.417	+	4.0798
03	**8c**	3.417	+	4.2074
04	**8d**	3.333	+	3.8568
05	**8e**	3.333	–	5.5227
06	**8f**	3.417	–	5.8122
07	**8g**	3.417	–	5.8122
08	**8h**	3.333	–	5.5894
09	Plain dopamine	3.5	+	
10	Plain levodopa	3.5	+	
11	(Levodopa + carbidopa)	3.083	+	

Dose: 200 mg/kg i.p.; neurotoxicity were measured after 30 min

(+) Indicates 50% or more passed the neurotoxicity test, i.e., not showing neurological disorder

(–) Indicates 50% or more failed the neurotoxicity test, i.e., showing neurological disorder

Discussion

Mach *et al*. (1999) reported a series of benzamide analogues possessing a high affinity for dopamine D_2 and D_3 receptors. Molecular modeling studies revealed

differences in the stereoelectronic properties of the oxadiazole binding region of the D_2 and D_3 receptors. These subtle differences in the electrostatic properties of this class of compounds suggested that isosteric replacement of the amide group with the heterocylic ring could produce a shift in affinity of these compounds for D_2 and D_3 receptors. These observations led to the synthesis and evaluation of a series of oxadiazole analogues as potential dopamine-receptor-selective ligands. Lipophilicity is thought to be a major determinant in the permeability of a drug. In order to correlate the permeability of the synthesized compounds to their lipophilicity, we performed the partitioning and log *P* studies, which confirmed that the compounds are more lipophilic in nature and should cross the blood–brain barrier (log $P > 2.6$) (Chu *et al*., 2005). Robert *et al.* (2003) suggested that the pyrole ring, which is a π-excessive heteroaromatic ring, represents a better isoteric substitution for the benzamide moiety than an imidazole ring, which π-deficient. Therefore we decided to test this hypothesis with another π-excessive heteroaromatic ring system, i.e., oxadiazole. The first goal of the current studies was to synthesize a number of oxadiazole analogues and evaluate them for dopamine receptors agonistic activity. The results of the above studies revealed that the oxadiazole analogues with affinity for the dopamine receptors act as agonists to reduce the degree of drug-induced catatonia. The second goal of the study was to determine to the effect on the location of the aromatic ring in the tertiary amine moiety on D2-like dopamine receptors binding. This type of compounds are also capable of forming intermolecular hydrogen bonds between the *ortho* and *para* methoxy groups with the receptors amino acid sequences and proton donor. Previous studies have suggested that the dopamine receptors have three aromatic binding pockets, named AR1, AR2, and AR3, as well as the site that recognizes basic nitrogen atoms. The benzamide aromatic ring containing compounds such as clebopride and sulpride are thought to bind to the AR1 aromatic pocket (primary aromatic binding site) while the benzylic aromatic group of MABN, IABN, and related compounds (e.g., clebopride and synthesized compounds) bind to either AR2 or AR3 regions (Ludtke *et al*., 2000). Therefore these oxadiazole derivatives showed lower activity profile than the combination of levodopa and carbidopa but greater activity profile than plain dopamine and levodopa. The in vivo studies revealed that none of the synthesized compounds caused any considerable reduction in the drug-induced catatonia compared to the combination of levodopa and carbidopa, but that all the compounds showed a greater reduction in drug-induced catatonia than dopamine or levodopa alone (Fig. 1). The results can be summarized as:

levodopa + carbidopa (3.083) = greater reduction in drug-induced catatonia.

8a, 8d, 8e, 8h (3.33) = less reduction in drug-induced catatonia than levodopa + carbidopa but more than **8b**, **8c**, **8f**, **8g**.

8b, **8c**, **8f**, **8g** (3.417) = less reduction in drug-induced catatonia than the compounds above but more than dopamine or levodopa alone.

Dopamine and levodopa alone did not show any reduction in drug-induced catatonia.

Compounds **8e**, **8f**, **8g**, and **8h** showed neurotoxicity.

In future these studies can help in the design and optimization of ligands with even greater potency/selectivity.

Experimental

Chemistry

Melting points were determined by open-capillary melting-point apparatus and were uncorrected. Elemental analysis of the synthesized compounds was carried out on a Carlo ERBA-1108 analyzer (Sophisticated Analytical Instrument Facility, Central Drug Research Institute, Lucknow) and the values were found to be within 4% of the theoretical values. ^{1}H nuclear magnetic resonance (NMR) spectral analysis of the synthesized compounds was recorded on a Brucker Advance DPX at 200 and 300 MHz (IICT Hyderabad and CDRI Lucknow) using $CDCl_3$ as a solvent and tetra methyl silane (TMS) as an internal reference unless stated otherwise; chemical shift values are expressed in δ parts per million (ppm). Fast atom bombardment/parts per million (FAB/ppm) mass spectra of the synthesized compounds were recorded on a JEOL (Tokyo, Japan) SX 102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 MA) as the FAB gas. Thin-layer chromatography (TLC) of the compounds was performed on precoated silica gel-G at a 0.2 mm thickness on aluminum sheet using a different solvent system to ascertain the purity of the synthesized compounds. Flash column chromatography on silica gel 230–400 mesh was used to purify the compounds. Iodine vapor and an ultraviolet (UV) lamp were used for detection.

All the starting materials and solvents were purchased from Aldrich, Fisher or Lancaster and were used without purification.

Synthesis of 2,3-dihydroxy-5-bromobenzoic acid (**2**)

To a solution of 2,3-dihydroxy benzoic acid (**1**, 25.0 g, 0.16 mol) in acetic acid (200 mL), bromine (25.9 g, 0.16 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight. Then the reaction, the reaction mixture was concentrated in vacuo to give a solid which was recrystallized from ethyl acetate/hexane to give 2,3-dihydroxy-5-bromobenzoic acid (**2**, 33.2 g, 88%), m.p. 202–204°C, lit. m. p. 204°C; anal. ($C_7H_5O_4Br$).

Synthesis of 2,3-dimethoxy-5-bromobenzoic acid (**3**)

A mixture of 2,3-dihydroxy-5-bromobenzoic acid (**2,** 25.0 g, 0.11 mol), dimethylsulfate (48.71 g, 0.38 mol), and potassium carbonate (53.4 g, 0.38 mol) in acetone (200 mL) was refluxed overnight. Then the reaction mixture was filtered, the filtrate was concentrated, and then dissolved in methanol (200 mL). To this solution, NaOH (40%, 12 mL) was added and the reaction mixture was refluxed for 2 h, the reaction mixture was concentrated and the residue was dissolved in water (200 mL). The pH of the aqueous phase was adjusted to δ 2 and then extracted with ethyl acetate (3 × 60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was further recrystallized from ethyl acetate/hexane to give 2,3-dimethoxy-5-bromobenzoic acid (**3,** 24.2 g, 86%), m.p. 199–200°C, lit. m. p. 200°C; analysis ($C_9H_9O_4Br$). ^{1}H NMR (300 MHz, $CDCl_3$): 7.84–7.85 (d, $J = 3$ Hz, 1 H), 7.25–7.26 (d, $J = 3$ Hz, 1 H), 4.07 (s, 3 H), 3.93 (s, 3 H).

Synthesis of 2,3-dimethoxy-5-bromobenzoyl chloride (**4**)

A solution of 2,3-dimethoxy-5-bromobenzoic acid (**3,** 20.0 g, 0.08 mol) and thionyl chloride (18.2 g, 0.15 mol) in benzene (200 mL) was refluxed over night. The reaction mixture was then concentrated and the residue was recrystallized from ethyl acetate/hexane to give 2,3-dimethoxy-5-bromobenzoyl chloride (**4,** 20.3 g, 95%), m.p. 65–66°C, analysis ($C_9H_8O_3BrCl$). ^{1}H NMR (300 MHz, $CDCl_3$): 7.61–7.62 (d, $J = 3$ Hz, 1 H), 7.23–7.24 (d, $J = 3$ Hz, 1 H), 3.90 (s, 6 H).

Synthesis of *N*-t-butyl-2,3-dimethoxy-5-bromo benzamide (**5**)

To a solution of (**4,** 20.0 g, 0.07 mol) in dry dichloromethane (200 mL) and t-butylamine (7.3 g, 0.1 mol), triethyl amine (5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature. Then the reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (100 mL). The organic layer was washed with 0.5 N NaOH in water and dried over Na_2SO_4, concentrated under reduced pressure. Purification of the crude reaction product by column chromatography on silica gel using hexane-EtOAc (4:1) as the eluant furnished the *N*-t-butyl-2,3-dimethoxy-5-bromo benzamide (**5**, 22.6 g, 96%) as a yellow syrup; analysis ($C_{13}H_{18}BrNO_3$).^{1}H NMR (300 MHz, $CDCl_3$): 7.78–7.77 (d, $J = 2.4$ Hz, 1 H), 7.11–7.10 (d, $J = 2.5$ Hz, 1 H), 3.86, 3.88 (2 s, 6 H), 1.45 (s, 9 H).

Synthesis of 2,3-dimethoxy-5-bromo benzonitrile (**6**)

To a solution of *N*-tert-butyl-2,3-dimethoxy-5-bromobenzamide (**8,** 22.6 g, 0.07 mol) in benzene (100 mL), phosphorus oxychloride (109 g, 0.7 mol) was added portionwise and the reaction mixture was refluxed for 10 h. Then the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with water, dried over Na_2SO_4, and concentrated under the reduced pressure. The residue was recrystallized from ethylacetate/pentane to give 2,3-dimethoxy-5-bromobenzonitrile (**6,** 15.3 g, 88%), analysis ($C_9H_8NO_2Br$). ^{1}H NMR (300 MHz, $CDCl_3$): 7.25–7.76 (d, $J = 3$ Hz, 1 H), 7.19–7.20 (d, $J = 3$ Hz, 1 H), 4.10 (s, 3 H), 3.89 (s, 3 H).

Synthesis of 2,3-dimethoxy-5-bromo benzamide oxime (**7**)

To the solution of 2,3-dimethoxy-5-bromobenzonitrile (**9,** 6.53 g, 0.04 mol) in ethanol (100 mL), hydroxylamine hydrochloride (8.34 g, 0.12 mol) and potassium carbonate (11.06 g 0.08 mol) were added and the reaction mixture was refluxed for 16 h. Then the reaction mixture was poured into cold water and 2 N NaOH was added to the solution to pH greater than 12. The product was extracted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from ethylacetate/hexane to give 2,3-dimethoxy-5-bromo benzamide oxime (**7**, 5.38 g, 68%), m.p. 148–150°C, analysis

($C_9H_{11}N_2O_3Br$). ^1H NMR (300 MHz, $CDCl_3$): 7.02–7.03 (d, 1 H), 7.19–7.20 (d, 1 H), 3.76 (s, 3 H), 3.89 (s, 3H), 2.0 (s, 2 H).

Typical procedure for the synthesis of compounds **8a-h**: 3-(5-bromo-2, 3-dimethoxy-phenyl)-5-(1-methyl-pyrrolidin-2-yl)-[1, 2, 4] oxadiazole (**8a**)

To a solution of 2,3-dimethoxy-5-bromo benzamide oxime (7, 1 g, 0.36 mmol) in tetrahydrofuran, NaH (0.09 g, 0.36 mmol) was added at 5°C. The reaction mixture was stirred at room temperature for 30 min. and then refluxed for one hour. After cooling the reaction mixture 1-methyl-pyrrolidine-2-carboxylic acid methyl ester, alumina, and HCOOH were added and the reaction mixture was refluxed over night. After completion of the reaction, the reaction mixture was poured into ice-cold water and extracted with CH_2Cl_2 (3 × 50 mL), washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude reaction product by column chromatography on silica gel using ethyl acetate/ethanol (3:2) solvent afforded the 3-(5-bromo-2,3-dimethoxyphenyl)-5-(1-methyl-pyrrolidin-2-yl)-[1, 2, 4] oxadiazole as a yellow syrup, which was converted into corresponding oxalic salt and recrystallized from ethyl acetate/ethanol; yield 62%; analysis $C_{15}H_{18}BrN_3O_3$, m.p. 63–65°C, found: C, 48.90; H, 5.24; N, 11.31; ^1H NMR (300 MHz, $CDCl_3$):^{TM} = 7.10 (s, 1 H,), 6.69 (s, 1 H,), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.52, 2.52 (m, 7 H,), 2.27 (s, 3 H, $NC\underline{H}_3$).

Synthesis of 3-[3-(5-bromo-2,3-dimethoxyphenyl)-[1, 2, 4] oxadiazol-5-yl]-1-methyl-piperidine (8b)

The derivative **8b** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, mol), 1-methyl-piperidine-2-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**. Yield (61%), analysis $C_{16}H_{20}BrN_3O_3$, m.p. 63–65°C, found: C, 50.17; H, 5.62; N, 10.89; ^1H NMR (300 MHz, $CDCl_3$): ^{TM} = 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 2.78–2.32 (m, 9 H), 2.27 (s, $C\underline{H}_3$).

Synthesis of 2-[3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazol-5-yl]-1-methyl-piperidine (**8c**)

The derivative (**8c**) was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-methyl-piperidine-1-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield 52%, analysis $C_{16}H_{20}BrN_3O_3$, m.p. 139–141°C, found: C, 50.20; H, 5.47; N, 10.89; ^1H NMR (300 MHz, $CDCl_3$): 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.02–2.32 (m, 9 H), 2.27 (s, $C\underline{H}_3$).

Synthesis of 4-[3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazol-5-yl]-1-methyl-piperidine (**8d)**

The derivative **8d** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-methyl-piperidine-3-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield 53%, analysis $C_{16}H_{20}BrN_3O_3$, m.p. 68–70°C, found: C, 50.17; H, 5.52; N, 10.85; ^{1}H NMR (300 MHz, $CDCl_3$): 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 2.74–2.32 (m, 9 H), 2.27 (s, $C\underline{H}_3$).

Synthesis of 5-(1-benzyl-pyrrolidin-2-yl)-3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazole (**8e**)

The derivative **8e** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-benzyl-pyrrolidine-2-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield 60%, analysis $C_{21}H_{22}BrN_3O_3$, m.p. 63–65°C, found: C, 56.67; H, 5.22; N, 9.36; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.14 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.62 (s, $C\underline{H}_2$), 3.53–2.50 (m, 7 H).

Synthesis of 1-benzyl-3-[3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazol-5-yl]-piperidine (**8f**)

The derivative **8f** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-benzyl-piperidine-3-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield (58%), analysis $C_{22}H_{24}BrN_3O_3$, m.p. 64–66°C, found: C, 57.60; H, 5.50; N, 9.07; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.14 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.62 (s, $C\underline{H}_2$), 2.78–1.79 (m, 9 H).

Synthesis of 1-benzyl-3-[3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazol-5-yl]-piperidine (**8g**)

The derivative **8g** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-benzyl-piperidine-2-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield 51%, analysis $C_{22}H_{24}BrN_3O_3$, m.p. 138–140°C, found: C, 57.60; H, 5.45; N, 9.07; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.14 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.62 (s, $C\underline{H}_2$), 3.02–1.50 (m, 9 H).

Synthesis of 1-benzyl-4-[3-(5-bromo-2,3-dimethoxy-phenyl)-[1, 2, 4] oxadiazol-5-yl]-piperidine (**8h**)

The derivative **8h** was synthesized using 2,3-dimethoxy-5-bromo benzamide oxime (**7,** 1 g, 0.36 mmol), NaH (0.09 g, 0.36 mmol), 1-benzyl-piperidine-4-carboxylic acid methyl ester, alumina, and HCOOH in tetrahydrofuran following the same procedure as discussed for compound **8a**; yield (54%), analysis $C_{22}H_{24}BrN_3O_3$, m.p. 70–71°C, found: C, 57.61; H, 5.45; N, 9.11; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.14 (m, 5 H), 7.10 (s, 1 H), 6.69 (s, 1 H), 3.73 (s, 6 H, $OC\underline{H}_3$), 3.62 (s, $C\underline{H}_2$), 2.74–1.50 (m, 9 H).

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