Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2017, 9(11):46-54

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and Evaluation of Benzimidazole Derivatives as Protein Tyrosine Phosphatase (PTP1B) Inhibitors

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ABSTRACT

Type-II Diabetes is characterized by insulin resistance in various tissues along with defect in pancreatic cells. Protein tyrosine phosphatases (PTPs) selectively dephosphorylate the tyrosine residues and regulate various cellular processes. Protein tyrosine phosphatase 1B (PTP1B) emerged as a novel target for Type -II diabetes due to its negative regulatory effect on insulin signaling. Studies on PTP1B knockout mice confirms PTP1B as an effective target for drug discovery process for anti-diabetic and anti-obesity agents. In the present study Benzimidazole derivatives linked with various heterocyclic moieties were synthesized. The structure of the synthesized compounds were confirmed by IR, NMR and Mass spectroscopy. The compounds were evaluated for PTP1B enzyme inhibition using Calbiochem® colorimetric assay kit. Among all synthesized compounds 4f-4j had shown good PTP1B inhibitory, while other compounds have shown lesser potency as an anti-diabetic agent.

Keywords: Type-II diabetes; Protein tyrosine phosphatase; PTP 1B; Benzimidazole

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INTRODUCTION

Type 2 diabetes, rapidly gaining the status of epidemic disease in India, is characterized by chronic hyperglycemia. Insulin resistance in peripheral tissues and in the liver, along with the defect in pancreatic cells, are the main cause of type 2 Diabetes (T2DM) [1,2]. Tyrosine phosphorylation and dephosphorylation controls most intracellular signaling processes, which are governed by protein tyrosine kinases (PTK) and Protein Tyrosine Phosphatases (PTPases) [3,4]. Protein tyrosine phospahatase, responsible for dephosphorylation of tyrosine residue are emerged as promising targets for various diseases including diabetes, obesity, autoimmune diseases, infectious diseases, inflammation, cancer, osteoporosis and neurodegeneration [5-11].

The type 2 diabetes is believed to be related to the defect in insulin receptor signaling. The insulin signaling start with binding of insulin with insulin receptor, which leads to receptor autophosphorylation and activation of protein tyrosine kinase [11]. The insulin signaling is negatively regulated by protein tyrosine phosphatases (PTP), which carry out the dephosphorylation of the receptor. Hence any defect in insulin signaling is possibly recovered by the inhibition of PTP ases [12]. The most likely candidates for treatment of type 2 diabetes include PTP1B, LAR, PTPa and SHP-2. Among these, PTP1B has been most intensively studied as a target for the development of inhibitors aiming at the treatment of type 2 diabetes and obesity. Protein tyrosine Phosphatase 1B (PTP1B) is a negative regulator of insulin signal transduction by dephosphorylation of tyrosine residue in regulatory domain of β-subunit of insulin receptor resulting in down regulation of insulin action. The studies with PTP1B knockout mice revealed improved insulin sensitivity and resistance to weight gain [13-19]. So, PTP1B inhibitors could reduce the insulin resistance and regulate the blood glucose level without causing hypoglycemia, and could emerged as a potential pharmacological agent for the treatment of obesity and T2DM.

In recent years, there is a huge rise in interest in development of small molecule PTP1B inhibitors with various heterocyclic nucleus [20]. Many heterocyclic rings have been explored as PTP1B inhibitors. Benzimidazole is an

important heterocyclic moiety due to its presence in wide variety of bioactive compounds. Moreover, many benzimidazole derivatives have been reported to show antidiabetic or PTP1B inhibitory activity. So, in this study, some benzimidazole derivatives linked with heterocyclic moieties were synthesized and evaluated for inhibitory activity on PTP1B enzyme.

EXPERIMENTAL SECTION

Chemical Studies

The targeted compounds were synthesized by various known procedures [21-24]. Our strategy for the synthesis of benzimidazole derivatives includes a reaction of p-halo anilines with acetic anhydride to produce p-haloacetanilides, which were nitrated to produce o-nitro, p-halo acetanilide's. The o-nitro, p-halo acetanilide's were hydrolyzed and subsequently reduced with sodium dithionate to produce 1,2-diamino, 4-halo benzene. These intermediates were cyclized by using chloroacetic acid, to form 5-substituted 2-chloromethyl benzimidazoles. These intermediates were treated with various heterocycles to form target compounds.

Synthesis of p-chloroacetanilide and p-fluoroacetanilide

0.05 mole of appropriate p-halo aniline was dissolved in 10 ml of acetic anhydride in a conical flask. The mixture was stirred at room temperature for 15 minutes. Soon the crystals of p-halo acetanilide's were begun to form. The mixture was poured in 50 ml cold water and the product was filtered. The precipitates were washed thoroughly with cold water. The product was almost pure and used for next step.

Synthesis of p-bromoacetanilide (1a-3a)

0.1 mole of acetanilide was dissolved in 15 ml of glacial acetic acid in a conical flask. In another flask 0.1 mole of bromine was mixed with 10 ml of glacial acetic acid. Bromine in acetic acid mixture was poured in to burette, and form burette it was drop by drop carefully added to acetanilide solution with constant stirring. When all the bromine was added, the solution turns to colorless or slightly orange colored due to the slight excess of bromine. The final reaction mixture was allowed to stand at room temperature for 30 minutes with occasional shaking. The reaction product was poured into 100 m1 of water; just sufficient amount of sodium metabisulphite solution was added to remove the orange color. The crystalline precipitates were filtered with suction and dried (Table 1).

Table 1: Physicochemical properties of compound 1a-3a

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. (reported)°C	Yield (%)
1	1a	C_8H_8ClNO	169	175-178(178-179)	80
2	2a	C_8H_8BrNO	213	167-169(165-169)	90
3	3a	C_8H_8FNO	153	151-154(153-155)	82

Synthesis of 4-halo-2-nitroacetanilide (1b-3b)

0.1 mole of 4-haloacetanilide was dissolved in 25 ml of cold sulphuric acid. The mixture was kept in ice bath and the temperature was maintained below 8°C. 7 ml of conc. Nitric acid was added dropwise to the above solution with constant stirring. Care was taken to maintain the temperature below 10°C, throughout the addition. The reaction mixture was allowed to stir for 30 minutes at room temperature. The mixture was poured in 250 ml cold water, with constant stirring. The yellow precipitates formed were collected and dried (Table 2).

Table 2: Physicochemical properties of compound 1b-3b

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. (reported)°C	Yield (%)
4	1b	$C_8H_7ClN_2O_3$	214	99-102(98-100)	60
5	2b	$C_8H_7BrN_2O_3$	259	101-103(102-104)	65
6	3b	$C_8H_7FN_2O_3$	198	72-74(72-73)	58

Synthesis of 4-halo-2-nitro-aniline (1c-3c)

A mixture of 0.1 mole of 4-halo-nitroacetanilide and 75 m1 of 50% w/w hydrochloric acid were boiled under a reflux condenser for 30 minutes or until a test sample remains clear upon dilution with 2-3 times its volume of water. The clear hot solution was poured into 200 ml of cold water and the 4-halo-2-nitroaniline was precipitated out by adding excess of 10 per cent sodium hydroxide solution. When cold, the yellow crystalline precipitates were filtered at the pump, washed with water and drain thoroughly.

Synthesis of 4-amino-3-nitroacetophenone (4c)

The 0.05 mole of 4-aminoacetophenone was mixed with 0.3 mole of calcium nitrate and 20 ml of glacial acetic acid, the mixture was irradiated with microwave radiation for 1 min at 150°C. The resultant mixture was poured into cold water and stored for some time in a refrigerator. The yellow crystals that separated were washed with water and allowed to dry. The compound was recrystallized from methanol (Table 3).

Table 3: Physicochemical properties of compound 1c-4c

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. (reported) °C	Yield (%)
7	1c	$C_6H_5ClN_2O_2$	172	115-117(117-119)	60
8	2c	$C_6H_5BrN_2O_2$	217	114-116(110-113)	58
9	3c	$C_6H_5FN_2O_2$	156	91-94(90-94)	58
10	4c	$C_8H_8N_2O_3$	180	156-158	45

Synthesis of 4-substituted benzene-1,2-diamines (p-Cl, p-Br, p-F, p-$COCH_3$) (1d-4d)

The 0.01 mole 4-substituted nitroaniline was dissolved in methanol (10ml/gm) in RBF attached with reflux condenser. The mixture was heated to 65°C. Portions wise 0.05 mole of sodium dithionate was added to it so that complete addition takes 30 minutes. The reaction mixture was refluxed for 1 hour during which color of the solution was changed from red orange to colorless. More sodium dithionate was added if needed to complete the reaction. When all of the nitro starting material is consumed, the reaction mixture was filtered to remove inorganic material. The filtrate was kept aside to facilitate evaporation of methanol. The residue is taken up in ethyl acetate and washed with water, brine, and dried over MgSO4, filtered, and concentrated to give the crude amine (Table 4).

Table 4: Physicochemical properties of compound 1d-4d

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. (reported)°C	Yield (%)
11	1d	$C_6H_7ClN_2$	142	68-70(70-73)	50
12	2d	$C_6H_7BrN_2$	187	66-69 (65-69)	48
13	3d	$C_6H_7FN_2$	126	80-85 (91-95)	50
14	4d	$C_8H_{10}N_2O$	150	105-107	35

Synthesis of 5-substituted 2-chloromethylbenzimidazoles (R= -Cl, -Br, -F, -$COCH_3$) (1e-4e)

0.01 mole of 4-substituted benzene-1,2-diamine was treated with 0.02 mole of chloro aceticacid and 25 ml of 4 N hydrochloric acid in a RBF, the reaction mixtures was heated under reflux for 45 minutes to 1 hour. The mixture was allowed to stand overnight, filtered, diluted with water, cooled and carefully neutralized with 6 N ammonium hydroxide solution. The solution was kept cold during the neutralization and stirred vigorously to prevent the formation of gums. The product was filtered, washed well with cold water and dried (Figure 1 and Table 5).

Table 5: Physicochemical properties of compound 1e-4e

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. (reported)°C	Yield (%)
15	1e	$C_8H_6Cl_2N_2$	201	217-219	60
16	2e	$C_8H_6ClBrN_2$	245	198-200	62
17	3e	$C_8H_6ClFN_2$	184	195-198	55
18	4e	$C_{10}H_9ClN_2O$	208	More than 250	40

Synthesis of 5-chloro2-methylsubstitutedbenzimidazole derivatives (1f-4k)

5-chloro-2-chloromethyl-1H-benzimidazole (0.025 mol), various heterocycles (0.025 mol) were separately dissolved in dioxane and mixed in a RBF, triethylamine (0.025 mol) was added and the reaction mixture was refluxed for 4 hrs. The reaction was monitored by TLC. The reaction mixture was then dumped in ice cold water and the precipitates were collected by suction and dried. The solid was recrystallized from ethanol (Figure 2 and Table 6).

The final compounds were confirmed by various spectral data. The spectral data of final compounds are summarized in Table 7.

Table 6: Physicochemical properties of compound 1f-4k

Sr. No.	Compound No.	Molecular formula	Mol. Wt. gm/mol	M.P. ºC	Yield (%)
19	1f	$C_{13}H_{17}ClN_4$	265	84-87	60
20	2f	$C_{13}H_{17}BrN_4$	309	80-82	63
21	3f	$C_{13}H_{17}FN_4$	248	75-77	56
22	4f	$C_{15}H_{20}N_4O$	272	120-123	43
23	5g	$C_{14}H_{19}ClN_4$	279	92-95	70
24	2g	$C_{14}H_{19}BrN_4$	323	84-86	72
25	3g	$C_{14}H_{19}FN_4$	262	80-83	68
26	4g	$C_{16}H_{22}N_4O$	286	135-138	45
27	1h	$C_{19}H_{21}ClN_4$	341	97-99	68
28	2h	$C_{19}H_{21}BrN_4$	385	90-92	65
29	3h	$C_{19}H_{21}FN_4$	324	80-82	66
30	4h	$C_{21}H_{24}N_4O$	348	142-145	48
31	1i	$C_{18}H_{19}ClN_4$	327	84-86	66
32	2i	$C_{18}H_{19}BrN_4$	371	75-78	64
33	3i	$C_{18}H_{19}FN_4$	310	80-82	65
34	4i	$C_{20}H_{22}N_4O$	334	122-125	47
35	1j	$C_{12}H_{14}ClN_3O$	252	67-69	65
36	2j	$C_{12}H_{14}BrN_3O$	296	65-67	68
37	3j	$C_{12}H_{14}FN_3O$	235	71-73	64
38	4j	$C_{14}H_{17}N_3O_2$	259	110-113	49
39	1k	$C_{12}H_{14}ClN_3$	236	64-66	67
40	2k	$C_{12}H_{14}BrN_3$	280	63-65	70
41	3k	$C_{12}H_{14}FN_3$	219	71-73	72
42	4k	$C_{14}H_{17}N_3O$	243	112-115	48

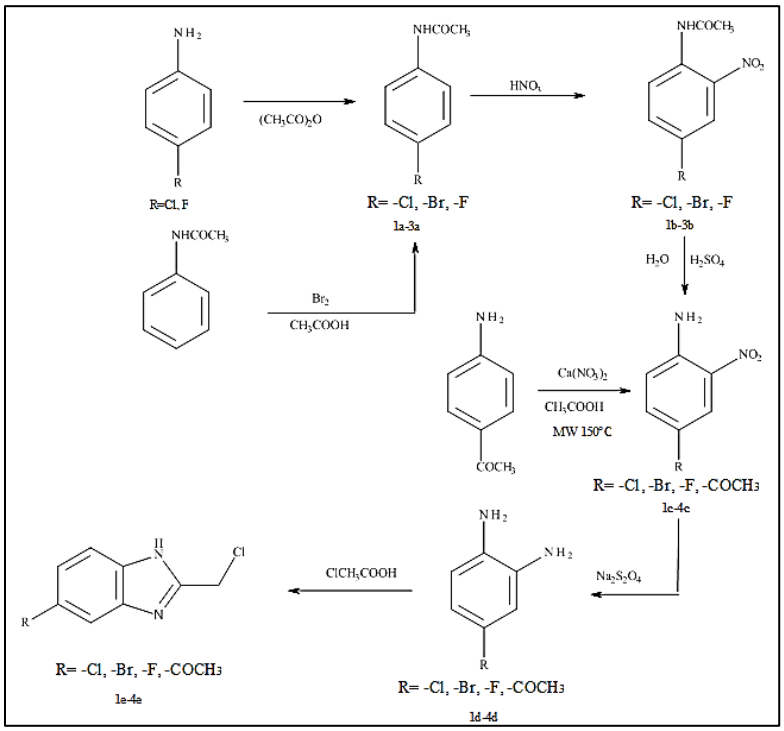

Figure 1: Synthetic scheme for compounds 1e-4e

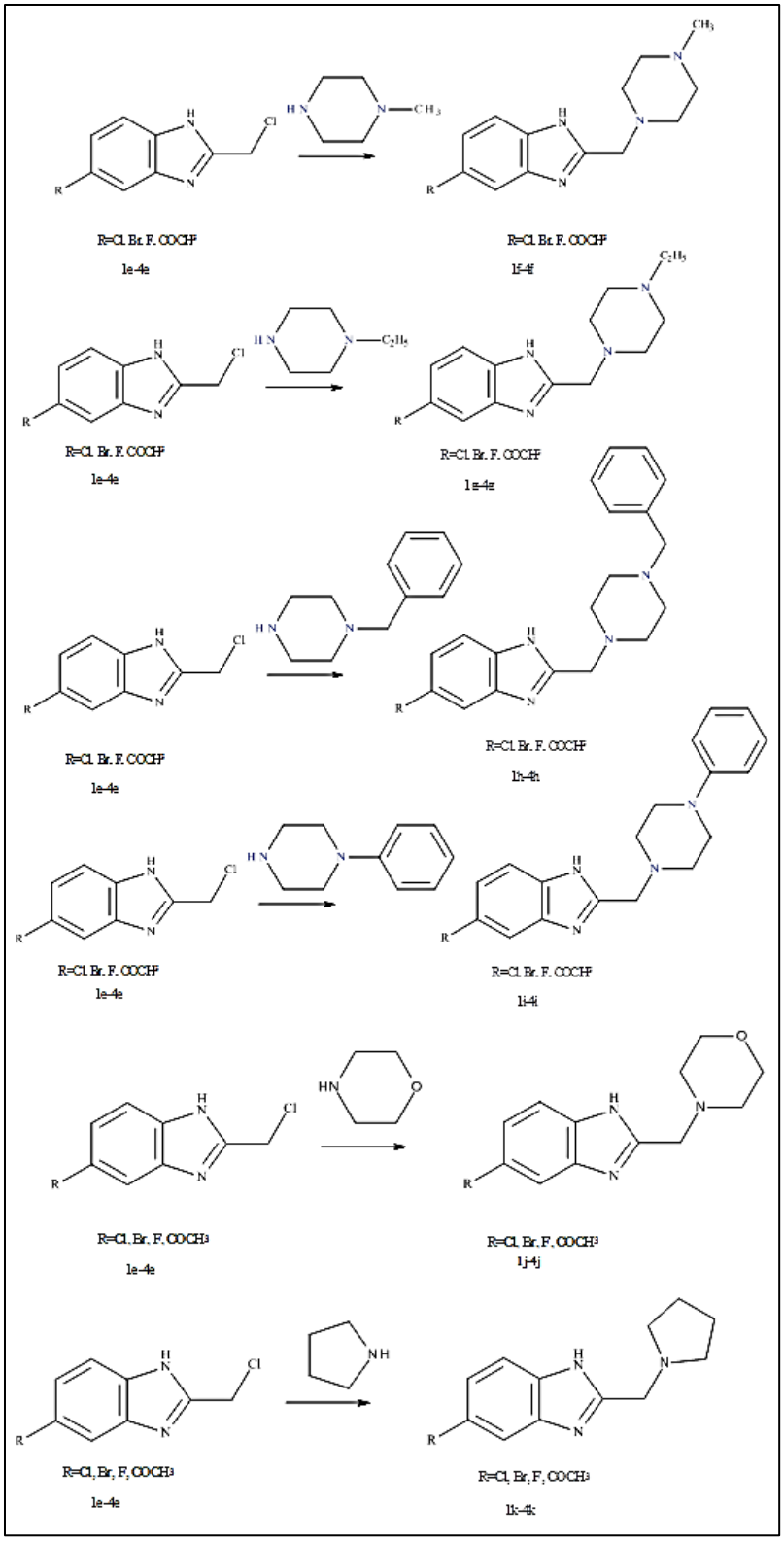

Figure 2: Synthetic scheme for compounds 1f-4k

Table 7: Spectral data of compound 1f-4k

Sr no.	Compound	IR stretching (cm-1)	^{1}H NMR	Mass (m/z)
1	1f	738 (C-Cl)	2.95 (s, 1H, -NH-),	264 (M^+),
		1370 (C-N)	7.14-8.36 (3H, Ar-H),	266 (M^{+2}), 165
		3015 (C-H, Ar)	4.43 (s, 2H, -CH_2-),	
			2.36-2.48 (m, 8H, -CH_2-),	
			2.26 (s, 3H, -CH_3)	
2	2f	585(C-Br)	2.45 (s, 1H, -NH-),	310 (M^{+2}),
		1373 (C-N)	7.14-7.87 (3H, Ar-H),	308 (M^+)
		3005(C-H, Ar)	4.45 (s, 2H, -CH_2-),	
			2.36-2.45 (m, 8H, -CH_2-),	
			2.24 (s, 3H, -CH_3)	
3	3f	1220 (C-F)	2.32 (s, 3H, N-CH_3)	248(M^+), 249 (M^{+1})
		1390 (C-N)	7.31-7.52(m, 3H, Ar-H)	
		3038 (C-H, Ar)	4.28 (s,1H, -CH_2-)	
			2.6 (m,8H, -CH_2- piperazine ring)	
4	4f	1722 (C=O)	2.38 (s, 1H, -NH-),	272(M^+), 273(M^{+1})
		1374 (C-N)	7.63-8.02 (3H, Ar-H),	
		1134 (C-N)	4.35 (s, 2H, -CH_2-),	
			2.65 (m, 8H, -CH_2-),	
			2.50 (s, 3H, -CO$\underline{CH_3}$)	
5	1g	736 (C-Cl)	7.32-7.61 (m,3H, Ar-H)	278(M^+), 280(M^{+1})
		1382 (C-N)	4.32 (s, 2H, -CH_2-)	
		1200 (C-N)	2.45 (q, 2H, J=6.5, -$\underline{CH_2}$-CH_3)	
			1.12(t, -CH_2-$\underline{CH_3}$)	
			2.51-2.62 (m, 8H, piperazine-CH_2)	
6	2g	2870 (-CH, Ali)	2.89 (s, 1H, -NH-),	322(M^+), 324(M^{+2})
		590 (C-Br)	7.23-8.34 (3H, Ar-H),	
			4.45 (s, 2H, -CH_2-),	
			2.36-2.48 (m, 8H, -CH_2-, piperazine),	
			1.15 (t, 3H, -CH_3)	
7	3g	1396 (C-N)	2.37 (s, 1H, -NH-),	262(M^+), 263 (M^{+1})
		1266 (C-N)	6.71-7.57 (3H, Ar-H),	
		1231 (C-F)	4.25 (s, 2H, -CH_2-),	
			2.48 (m, 8H, -CH_2-, piperazine), 1.17(t, 3H, -CH_3)	
8	4g	1726 (C=O)	2.45 (q, 2H, , -$\underline{CH_2}$-CH_3),	286(M^+), 287((M^{+1})
		1338 (C-N)	0.960 (t, 3H, -CH_2-$\underline{CH_3}$)	
		1110 (C-N)	2.3 (s,3H, -CO-CH_3)	
			4.36 (s, 2H, -CH_2-)	
			7.8-8.2 (m,3H, Ar-H)	
			2.5-2.6 (m, 8H, piperazine-CH_2)	
9	1h	742 (C-Cl)	7.23-8.36 (8H, Ar-H),	340 (M^+), 342(M^{+2})
		1325 (C-N)	3.66 (s, 2H, -CH_2-),	
		1200 (C-N)	2.48 (m, 8H, -CH_2-, piperazine),	
			4.43 (s, 2H, -CH_2)	
10	2h	582 (C-Br)	4.21 (s, 2H, -CH_2-)	384 (M^+), 386 (M^{+2})
		1340 (C-N)	3.61 (s, 2H, Benzylic –CH_2)	
		3080 (-CH Ar)	7.23-8.01 (m,8H, Ar-H)	
			2.63-2.72 (m, 8H, piperazine)	
11	3h	1254 (C-F)	4.22 (s, 2H, -CH_2-)	324 (M^+), 325(M^{+1})
		1301 (C-N)	3.62 (s, 2H, Benzylic –CH_2)	
		3041 (C-H)	7.24-8.11 (m,8H, Ar-H)	
			2.63-2.72 (m, 8H, piperazine)	
12	4h	1700 (-CO-)	2.35 (s, 3H, -CH_3)	348(M^+), 349(M^{+1})
		3085 (Ar-H)	8.00-8.21 (m, 3H, Ar-H)	
			7.23-7.51 (m, 5H, Ar-H)	
			3.65 (s, 2H, benzylic –CH_2-)	
			4.42 (s, 2H, -CH_2-)	
			2.34 (s, 3H, -CH_3-)	
			2.54-2.78 (m, 8H, -piperazine)	
13	1i	680 (C-Cl)	6.79-8.37 (m, 8H, Ar-H)	326(M^+), 328(M^{+2})

		2800-2850 (-CH- Ali)	3.20-2.71 (t & t, 8H, piperazine)	
		3090 (Ar -CH-)	4.31 (s, 2H, -CH_2-)	
14	2i	725 (C-Br)	4.25 (s, 2H, -CH_2-)	370(M^+), 372(M^{+2})
		1380 (C-N)	7.23-7.55 (m,8H, Ar-H)	
		1216 (C-N)	2.78- 3.19 (m, 8H, piperazine)	
15	3i	1260 (C-F)	4.32 (s, 2H, -CH_2-),	310($^{M+}$), 311($^{M+1}$)
		2872 (CH, Aliphatic)	6.69-7.57 (m, 8H, Ar-H)	
		3078 (CH, Aromatic)	3.19-2.71 (t, 8H, Piperazine)	
			4.20 (s, 2H, -CH_2-)	
			2.31 (s, 1H, -NH-)	
16	4i	1732 (C=O)	4.42 (s, 2H, -CH_2-)	334(M^+), 335(M^{+1})
		1380 (C-N)	6.69-8.02 (m, 8H, Ar-H)	
		1112 (C-N)	3.18-2.72 (t, 8H, Piperazine)	
		3093 (Ar C-H)	4.42 (s, 2H, -CH_2-)	
			2.52 (s, 3H, -CH_3-)	
17	1j	685 (C-Cl)	7.63-8.18 (m, 3H, Ar-H)	251(M^+), 253(M^{+2})
			4.35 (s, 2H, -CH_2)	
			2.56 (m, 4H, Morpholine)	
			3.64 (m, 4H, Morpholine)	
18	2j	727 (C-Br)	7.53-8.36 (m, 3H, Ar-H)	295(M^+), 297(M^{+2})
		2855 (CH, Aliphatic)	2.50 (m, 4H, Morpholine)	
		3022 (CH, Aromatic)	3.65 (t, 4H, Morpholine)	
		1088 (ether)	4.46 (s, 2H, -CH_2-)	
19	3j	1225 (C-F)	6.97-7.57 (m, 3H, Ar-H)	235(M^+), 236(M^{+1})
		2860 (C-H, Aliphatic)	2.50 (m, 4H, Morpholine)	
		3020 (CH, Aromatic)	3.64 (t, 4H, Morpholine)	
		1090 (ether)	4.42 (s, 2H, -CH_2-)	
20	4j	1115 (C-O-C)	2.32 (s, 3H, -CH_3)	259(M^+), 260(M+1)
		1291 (C-N)	7.51-8.25 (m, 3H, Ar-H)	
		1673 (C=O)	4.45 (s, 2H, -CH_2-)	
			2.55 (m, 4H, Morpholine)	
			3.63 (m, 4H, Morpholine)	
21	1k	820 (C-Cl)	4.34 (s, 2H, -CH_2-)	235(M^+), 237(M+2)
		1325 (C-N)	7.25-8.85 (m, 3H, Ar-H)	
			2.58 (m, 4H, Pyrrolidine)	
			2.13 (m, 4H, Pyrrolidine)	
22	2k	570 (C-Br)	7.21-7.58 (m, 3H, Ar-H)	279(M^+), 281(M+2)
		2850 (C-H, Aliphatic)	4.32 (s, 2H, -CH_2-)	
			3.05 (m, 4H, pyrrolidine)	
			2.15 (m,4H, pyrrolidine)	
23	3k	1220 (C-F)	7.01-7.59 (m, 3H, Ar-H)	219(M^+), 220(M+1)
		2860 (C-H, Aliphatic)	3.11 (m, 4H, Pyrrolidine)	
			2.12 (m ,4H, Pyrrolidine)	
			4.31 (s, 2H, -CH2-)	
24	4k	1668 (C=O)	7.51-8.23 (m, 3H, Ar-H)	243(M^+), 244(M+1)
		2860 (C-H, Aliphatic)	4.33 (s, 2H, -CH_2-)	
			2.43 (s, 3H, -CH_3-)	
			3.12 (m, 4H, pyrrolidine)	
			2.13 (m,4H, pyrrolidine)	

Biological Study

All the synthesized compounds were evaluated for PTP-1B inhibitory activity using Calbiochem® PTP1B colorimetric assay kit. In the inhibitory study, Suramin, a protein based PTP1B inhibitor was taken as a control. The test sample and suramin were assayed for PTP1B inhibitory activity using final concentration of 10 µM in each well [25,26]. The phosphate standard curve data and PTP inhibitory data are summarized in Tables 8 and 9 respectively (Figure 3).

Table 8: Absorbance data for phosphate standard curve

Concentration of phosphate (nmol)	Absorbance at 620 nm
0	0.009
0.25	0.011
0.5	0.063
1	0.214
2	0.557
3	0.854

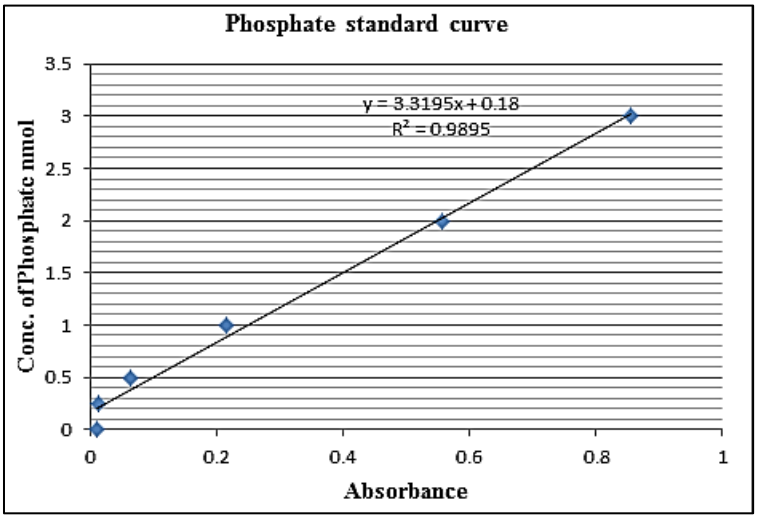

Figure 3: Phosphate standard curve

Table 9: % inhibition as compared to time zero and suramin of compound

Compound No	Absorbance at 620 nm	nmole of phosphate	% inhibition compare to Time zero	% inhibition compare to suramin
Suramin	0.153	0.6878	84.296	100
1f	0.553	2.0154	39.745	47.15
2f	0.54	1.9722	41.2	48.87
3f	0.555	2.022	39.53	46.89
4f	0.348	1.335	62.58	74.23
5g	0.579	2.1017	36.849	43.71
2g	0.569	2.0685	37.97	45.04
3g	0.534	1.9523	41.87	49.67
4g	0.367	1.398	60.47	71.73
1h	0.568	2.0651	38.075	45.16
2h	0.498	1.8328	45.88	54.42
3h	0.564	2.0519	38.52	45.69
4h	0.324	1.2553	65.25	77.4
1i	0.352	1.3482	62.14	73.71
2i	0.512	1.8793	44.32	52.57
3i	0.527	1.9291	42.65	50.59
4i	0.348	1.335	62.58	74.23
1j	0.542	1.9788	40.97	48.6
2j	0.576	2.0917	37.19	44.11
3j	0.549	2.0021	40.2	47.68
4j	0.364	1.3881	60.8	72.12
1k	0.551	2.008	39.968	47.41
2k	0.601	2.1747	34.4	40.8
3k	0.586	2.1249	36.07	42.78
4k	0.412	1.5474	55.45	65.78

CONCLUSION

The benzimidazole derivatives were synthesized and evaluated for PTP1Binhibitory activity. The yield of the synthesized compounds ranged from 40-70%. There structures of the title compounds were confirmed by IR, NMR and Mass spectroscopy. PTP1B inhibitory data reveals that the compounds 4a-4k containing -$COCH_3$ group show good inhibitory activity against PTP1B. While the compounds which contain -Cl, -Br or -F group attached to benzimidazole ring shown moderate PTP1B inhibitory activity. So, it can be concluded that, electron withdrawing groups attached to benzimidazole ring shows lesser PTP1B inhibitory activity.

ACKNOWLEDGEMENT

The authors express their gratitude towards the Principal, Management and A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar and SICART managed by Charutar Vidya Mandal for providing necessary facilities to carry out this work.

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