

## Synthesis and antidiabetic evaluation of some novel compounds

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Aryloxypropanolamines have been reported to have  $\beta_3$ -agonist activity. Agonists of  $\beta_3$ -adrenergic receptors have been observed to simultaneously increase lipolysis, fat oxidation, energy expenditure and insulin action leading to the belief that this receptor might serve as an attractive target for the treatment of diabetes and obesity. Various aryloxypropanolamine derivatives have been synthesized starting with the substituted imines derived from 4-hydroxy benzaldehyde and substituted anilines. These imines have been converted to benzamide intermediates. The benzamide epoxide intermediates have been synthesized using epichlorhydrin. The title compounds **6a-j** have been synthesized *via* ring opening of the epoxides. The synthesized compounds have been characterized using infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry. The synthesized compounds have been evaluated for antidiabetic activity on streptozotocin induced diabetic male Wistar rats. The synthesized aryloxypropanolamine derivative consisting of  $-\text{OCH}_3$  and *t*-butyl amine substituents show good activity as compared to the other synthesized compounds in the series. Glibenclamide has been taken as standard for measuring the antidiabetic activity.

**Keywords:** Aryloxypropanolamines, antidiabetic activity, lipolysis, streptozotocin, glibenclamide

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both<sup>1-4</sup>.

Currently anti-diabetic drugs used in long term therapy are found to be associated with various toxicities owing to which the development process in the anti-diabetic drug discovery has shifted its focus to newer anti-diabetic agents<sup>5,6</sup>. Current therapies for type II diabetes have inherent problems including non compliance, ineffectiveness and hypoglycemic episodes with insulin and sulphonyl ureas<sup>7</sup>.

The  $\beta_3$ -adrenergic receptor ( $\beta_3$  AR) is a G-protein coupled seven trans-membrane domain receptor that is expressed mainly in the adipose tissues where the excess fats are stored<sup>8-10</sup>. The stimulation of  $\beta_3$  AR agonist has also been found to cause insulin sensitization<sup>11</sup>.

Aryloxypropanolamine such as Pindolol **1** and Propranolol **2** (Figure 1) are well known for their ability to antagonize  $\beta$ -adrenoreceptor antagonist activity<sup>12</sup>.

Aryloxypropanolamine, aryl group with oxirane side chain attached with primary or secondary amine

have diverse pharmacological activities like anti-convulsant, anti-hypertensive, anti-obesity, and cardiovascular diseases<sup>13-15</sup>. Hence it was decided to take up the synthesis of newer derivatives of aryloxypropanolamines and screening of the same for anti-diabetic activity.

### Result and Discussion

The formation of imine **3** using 4-hydroxybenzaldehyde **1** and substituted aniline **2** reaction by the removal of water molecule. The imine intermediate **3** with benzoyl chloride which contains chloride group which withdraws the electron density towards itself and also the oxygen atom present on it pulls the electron towards itself creating the positively charged carbon nuclei. There is the formation of benzamide intermediate **4**. Further the benzamide intermediate **4** with the epichlorhydrin molecule the oxirane intermediate **5** was formed. The intermediate then reacts with the amine like isopropylamine, butylamine, diethylamine or piperidine to form hydroxyl group on secondary carbon atom with the nitrogen attached to the terminal

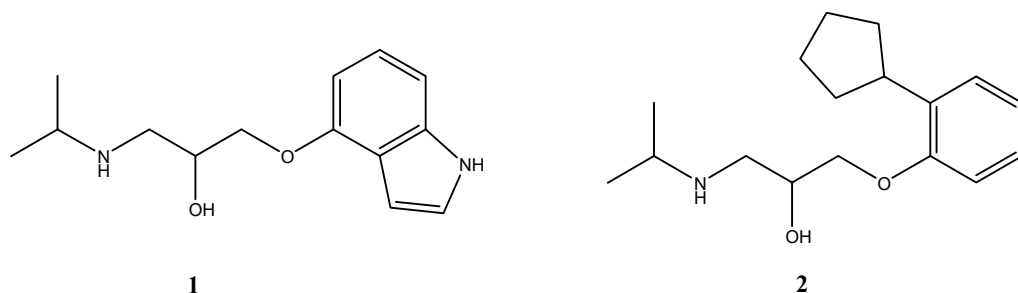


Figure 1

carbon atom forming the skeleton of the aryloxypropanolamine derivative **6a-f** (Scheme I).

### Biological Evaluation

The synthesized aryloxypropanolamine derivatives were evaluated for their anti-diabetic activity. The activity was performed on the Streptozotocin (STZ) induced diabetic rats.

The intraperitoneal injection of 65 mg/kg body weight of STZ was given to the overnight fasted male Wistar rats. It caused necrosis or the complete or partial destruction of the beta cells of Islet of Langerhans in the rats. Further it produces the diabetes within 72 h. The blood glucose level was checked by using "Accu-check Sensor Comfort" glucometer strips on Roche glucometer.

The standard drug Glibenclamide was used which shows about 50% blood glucose lowering level and effective oral hypoglycemic activity. All the synthesized aryloxypropanolamine derivatives were suspended in the 0.3% of sodium carboxy methyl cellulose in distilled water. The anti-diabetic activities of synthesized compounds were compared with the standard Glibenclamide.

The blood glucose level was measured at 0, 0.5, 1, 2, 3, 4, 5 and 6 h intervals (Figure 2). The percent decrease in blood glucose level from 0 to 6 h by the test sample was calculated. Of these six synthesized compounds, N-((1S)-4-(3-(tert-butylamino)-2-hydroxypropoxy) phenyl) chloromethyl-N-(3-methoxyphenyl)benzamide **6e**, showed 50.64% and 77.09% decrease in blood glucose level after 2 h and 6 h respectively (Table I). The electron donating groups present on the *meta* position of the aniline have been shown to increase the agonistic activity, thereby increasing the anti-diabetic activity. The synthesized compound **6e** having  $-\text{OCH}_3$  group has shown highest activity.

The synthesized compound **6e** consists of *t*-butylamine on oxypropylamine side chain, but the

synthesized compound **6c** consisting of similar *t*-butylamine group and disubstituted aniline has shown less activity. The synthesized compound **6f** consisting of electron donating nitro group on *meta* position and diethylamine has shown good activity.

Synthesized compounds **6a**, **6b** and **6d** consisting of aniline-isopropylamine, *p*-chloroaniline-piperidine and *o*-toluidine-diethylamine respectively have shown moderate antidiabetic activity.

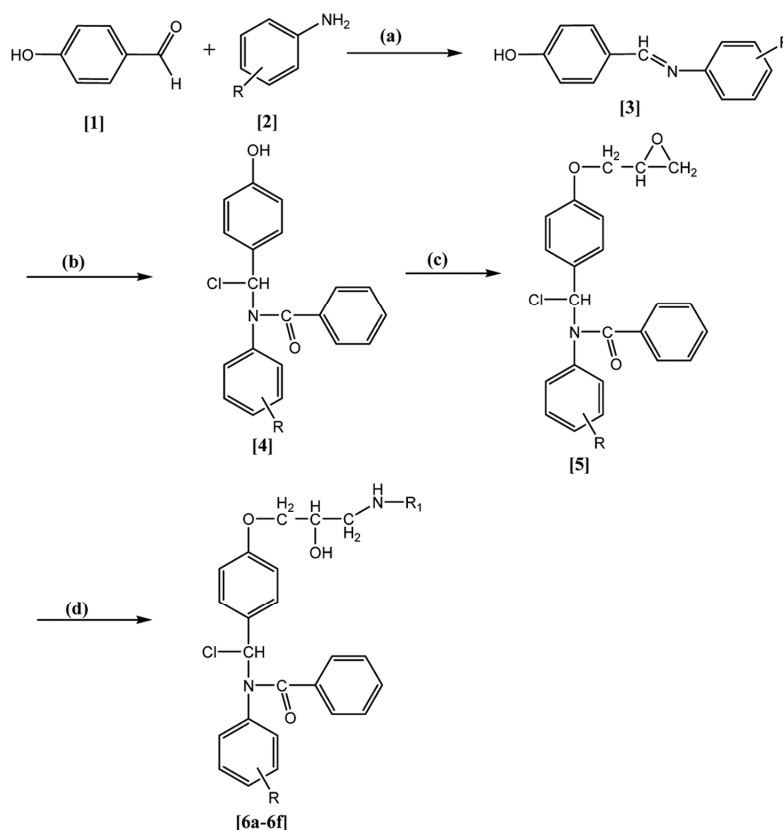
The results reveal that the synthesized compounds show moderate anti-diabetic activity, as compared to standard drug *i.e.* Glibenclamide.

### Experimental Section

Melting points of synthesized organic compounds were determined on VEEGO-VMP I melting point apparatus and are uncorrected; IR spectra were recorded on JASCO-FTIR 4100 spectrophotometer.  $^1\text{H}$  NMR were recorded using Varian Mercury 300 MHz instrument. Chemical shifts ( $\delta$ ) are reported in parts per million ( $\delta$ , ppm) with  $\text{CDCl}_3$  ( $\delta$  7.26) as solvent. Tetramethylsilane (TMS) was used as internal standard for NMR. Mass spectra were also recorded. Thin Layer Chromatography was performed on aluminium plate pre-coated with Silica Gel 60 F254.

### General procedure for the preparation of imine derivatives, 3a-f

The substituted aniline (0.0329 mol, 1 equiv.) was dissolved in methanol (20 mL, 4 vol.) in a beaker and in a round bottom flask 4-hydroxy benzaldehyde (0.0329 mol, 1 equiv.) was dissolved in methanol (20 mL, 4 vol.) with continuous stirring. The solution of substituted aniline was slowly added drop by drop in to the solution of 4-hydroxybenzaldehyde with continuous stirring. On completion of addition, the mixture was allowed to reflux for 1-4 h as per the requirement with continuous monitoring on TLC at intervals of every 30 min. After completion of



**Reaction conditions:** (a) Methanol (MeOH), Reflux for 4 h, (b) Dimethyl foramide (DMF), Benzoyl chloride, (c) Sodium hydride(NaH), DMF, Epichlorhydrin, (d) MeOH, R<sub>1</sub>-NH<sub>2</sub>, Reflux

Scheme I — Synthesis of arylpropoxylamine derivatives

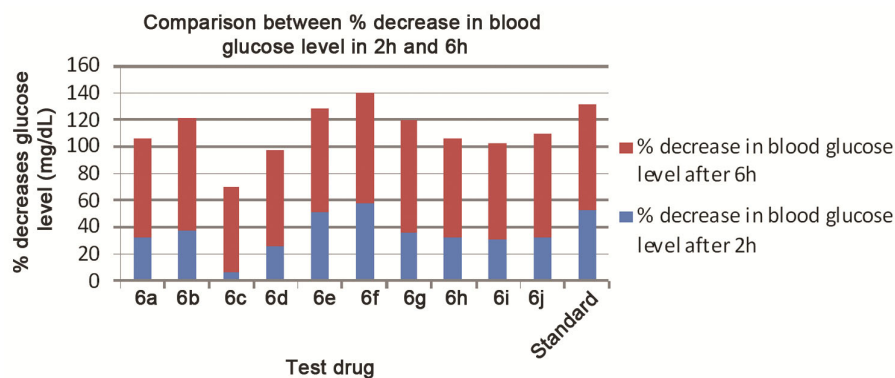


Figure 2 — Comparison between percent decrease in blood glucose level in 2 h and 6 h

reaction, the reaction mixture was poured in to an evaporating dish and the solvent allowed to evaporate or the excess of solvent was removed under reduced pressure. The solid was isolated and melting point of the obtained imine was determined.

**4-((Phenylimino)methyl)phenol, 3a:** Yield 85.22%. Mol. Formula: C<sub>13</sub>H<sub>11</sub>NO. Mol. Wt. 197.23. m.p.120-123°C. R<sub>f</sub>: 0.63(Hexane: ethyl acetate, 1:0.5); IR (KBr): 3050-3000 (aromatic hydrocarbon), 2869 (C-H

str.), 2210-2260 (C=N), 1710-1690 (Ar-CHO), 1400 (alkene C-H bend), 1180-1360 cm<sup>-1</sup> (amines); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7-7.5(m, 5H, aromatic H), 5.5(d, -OH), 7.52 (m,benzylidenimin).

**4-(((4-Chlorophenyl)imino)methyl)phenol, 3b:** Yield 87.53%. Mol. Formula: C<sub>13</sub>H<sub>10</sub>ClNO. Mol. Wt.231.68. m.p.108°-183°C. R<sub>f</sub>: 0.57 (Hexane: Ethyl acetate, 1:0.5); IR (KBr): 3050-3000 (aromatic hydrocarbon), 2869 (C-H str.), 2210-2260 (C=N),

Table I — Percent decrease in blood glucose level after 2 h and 6 h

S.No	Product	R	R <sub>1</sub>	Decrease in blood glucose level (%)	
				After 2 h	After 6 h
1	<b>6a</b>	-H		32.044	74.58
2	<b>6b</b>	4-Cl		37.19	84.54
3	<b>6c</b>	3,4-dichloro		6.63	62.97
4	<b>6d</b>	2-CH <sub>3</sub>		25.87	72.13
5	<b>6e</b>	3-OCH <sub>3</sub>		50.64	77.09
6	<b>6f</b>	3-NO <sub>2</sub>		58.64	80.93
7	<b>6g</b>	-H		36.22	82.62
8	<b>6h</b>	3,4-dichloro		33.01	73.24
9	<b>6i</b>	2-CH <sub>3</sub>		30.54	72.66
10	<b>6j</b>	3-OCH <sub>3</sub>		32.68	75.77
	Standard Glibenclamide			53.26	78.10

1710-1690 (Ar-CHO), 1400 (alkene C-H bend), 1180-1360 cm<sup>-1</sup> (amines); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 6.35(singlet, OH), 7.5-7.8(multiplet of benzene), 2.34 (singlet, 3H, methyl).

**4-(((3,4-Dichlorophenyl)imino)methyl)phenol, 3c:** Yield 92.33%. Mol. Formula: C<sub>13</sub>H<sub>9</sub>C<sub>12</sub>NO. Mol. Wt. 266.12. m.p.185°-190°C. R<sub>f</sub>: 0.56 (Hexane: ethyl acetate, 1:0.6); IR (KBr): 3439.19, 3.63.06 (aromatic hydrocarbon), 2837.38 (C-H stretching), 1863.3,

1597.11, 1429.95 (alkene C-H bend), 1379.15, 1242.20 (amines), 1035.81, 976.01, 819.77 cm<sup>-1</sup>.

**4-((*m*-Tolylimino)methyl)phenol, 3d:** Yield 89.22%. Mol. Formula: C<sub>14</sub>H<sub>13</sub>NO. Mol. Wt. 211.26. m.p.182°-187°C. R<sub>f</sub>: 0.51 (Hexane: ethyl acetate, 1:0.5); IR (KBr): 3050-3000 (aromatic hydrocarbon), 2869 (C-H str.), 1600-1700 (C=N stretch), 1400 (alkene C-H bend), 1300-1500 (C-H bending), 1171-1690 (Ar-CHO), 1180-1360 cm<sup>-1</sup> (amines).

**4-(((3-Methoxyphenyl)imino)methyl)phenol, 3e:** Yield 97.01%. Mol. Formula: C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>. Mol. Wt. 227.26. m.p.182°-187°C. R<sub>f</sub>: 0.54 (Hexane: ethyl acetate, 1:0.5).

**4-(((3-Nitrophenyl)imino)methyl)phenol, 3f:** Yield 94.64%. Mol. Formula: C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>. Mol. Wt. 242.23. m.p.185°-187°C. R<sub>f</sub>: 0.52 (Hexane: ethyl acetate, 1:0.5).

#### General procedure for the preparation of benzamide derivatives, 4a-f

The imine (0.01 mol, 1 eq.) was dissolved in dimethyl formamide (20 mL) with continuous stirring. The addition of benzoyl chloride (0.02 mol, 2 eq.) was done in the above solution at 0 to 5°C temperature. Stirring was continued at RT for 32-36 h. Formation of acid chloride was observed by thin layer chromatography (TLC). After completion of the reaction, the solution of DMF was quenched in 10 volume of ice-cold water, the solid compound precipitated out, and its formation confirmed by TLC and melting point. If solid did not precipitate out then it was extracted by using ethyl acetate solvent. Further the ethyl acetate extract was treated with brine solution. Then the ethyl acetate removed by vacuum distillation, leaving the acid chloride as residue.

**N-(Chloro(4-hydroxyphenyl)methyl)-N-phenylbenz- amide, 4a:** Yield 65%. Mol. Formula: C<sub>20</sub>H<sub>16</sub>ClNO<sub>2</sub>. Mol. Wt. 337.80. m.p.132-136°C. R<sub>f</sub>: 0.62 (Hexane: ethyl acetate, 1:0.5); IR (KBr): 3153, 2977, 1588, 1510, 1365, 1159, 1086, 756, 700 cm<sup>-1</sup>.

**N-(Chloro(4-hydroxyphenyl)methyl)-N-(4-chloro- phenyl) benzamide, 4b:** Yield 60.52%. Mol. Formula: C<sub>20</sub>H<sub>15</sub>Cl<sub>2</sub>NO<sub>2</sub>. Mol. Wt. 372.24. m.p.86-90°C. R<sub>f</sub>: 0.60 (Hexane: ethyl acetate, 1:0.5); IR (KBr): 3180, 2990, 1584, 1536, 1428, 1336, 1236, 1208, 1188, 1144, 1088, 996, 884, 780, 744 cm<sup>-1</sup>.

**N-(Chloro(4-hydroxyphenyl)methyl)-N-(3,4-dichloro- phenyl) benzamide, 4c:** Yield 65.83%. Mol. Formula: C<sub>20</sub>H<sub>14</sub>Cl<sub>3</sub>NO<sub>2</sub>. Mol. Wt. 406.69. m.p.100-102°C. R<sub>f</sub>: 0.78 (Hexane: ethyl acetate,

1:0.5); IR (KBr): 3180, 2950, 1590, 1500, 1476, 1352, 1316, 1280, 1175, 1148, 1100, 1024, 1004, 960, 896, 795, 756  $\text{cm}^{-1}$ .

**N-(Chloro(4-hydroxyphenyl)methyl)-N-(*o*-tolyl) benzamide, 4d:** Yield 69.51%. Mol. Formula:  $\text{C}_{21}\text{H}_{18}\text{ClNO}_2$ . Mol. Wt. 351.83. m.p.110-114°C.  $R_f$ : 0.8 (Hexane: ethyl acetate, 1:0.5).

**N-(Chloro(4-hydroxyphenyl)methyl)-N-(3-methoxyphenyl) benzamide, 4e:** Yield 80.20%. Mol. Formula:  $\text{C}_{21}\text{H}_{18}\text{ClNO}_3$ . Mol. Wt. 367.83. m.p.96-110°C.  $R_f$ : 0.64 (Hexane: ethyl acetate, 1:0.5); IR (KBr): 3411,2978,2932,1504,1436,1243,1113, 1024, 775, 743, 701  $\text{cm}^{-1}$ .

**N-(chloro(4-hydroxyphenyl)methyl)-N-(3-nitrophenyl) benzamide, 4f:** Yield 86.32%. Mol. Formula:  $\text{C}_{20}\text{H}_{15}\text{ClN}_2\text{O}_4$ . Mol. Wt. 382.80. m.p.78-82°C.  $R_f$ : 0.52 (Hexane: ethyl acetate, 1:0.5); IR (KBr): 3222, 2983, 1564, 1518, 1489, 1343, 1301, 1286, 1147, 1090, 1072  $\text{cm}^{-1}$ .

#### General procedure for the preparation of oxirane derivatives, 5a-f

The step 2 benzamide (0.1mol, 1 equivalent) was dissolved in dimethyl formamide (0.4 mol, 4 equivalent) with continuous stirring. Sodium hydride base was added (0.1 mol, 1 equivalent) in the above solution at 0-5°C and the mixture allowed to stir for 10-15 min. Epichlorhydrin (0.4 mol, 4 equivalents) was added drop by drop at RT. The mixture was allowed to stir for 8-12 h as per the requirement of the reaction. Reaction was monitored by thin layer chromatography from time to time. After completion of the reaction, the reaction mixture in DMF was poured in to 10 volumes of ice-cold water. If solid precipitated out then it was filtered out and if not, the aqueous solution was extracted with ethyl acetate. The ethyl acetate extract was washed with brine solution. The oxirane intermediate was obtained by vacuum distillation of ethyl acetate.

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-phenylbenzamide, 5a:** Yield 42.5%. Mol. Formula:  $\text{C}_{23}\text{H}_{20}\text{ClNO}_3$ . Mol. Wt. 393.86. m.p.99.105°C.  $R_f$ : 0.48(chloroform: methanol, 1:0.2).

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-(4-chlorophenyl) benzamide, 5b:** Yield 77.10%. Mol. Formula:  $\text{C}_{23}\text{H}_{19}\text{Cl}_2\text{NO}_3$ . Mol. Wt. 428.31, Melting point:85-90°C.  $R_f$ : 0.48 (chloroform: methanol, 1:0.2).

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-(3,4-dichlorophenyl) benzamide, 5c:** Yield 53.30%. Mol. Formula:  $\text{C}_{23}\text{H}_{18}\text{Cl}_3\text{NO}_3$ . Mol.

Wt. 462.75. m.p.120-123°C.  $R_f$ : 0.52 (chloroform: methanol, 1:0.2).

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-(*o*-tolyl) benzamide, 5d:** Yield 54.63%. Mol. Formula:  $\text{C}_{24}\text{H}_{22}\text{ClNO}_3$ . Mol. Wt. 407.89. m.p.130-136°C.  $R_f$ : 0.76 (chloroform: methanol, 1:0.2).

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-(3-methoxyphenyl) benzamide, 5e:** Yield 60.86%. Mol. Formula:  $\text{C}_{24}\text{H}_{22}\text{ClNO}_4$ . Mol. Wt. 423.89. m.p.70-74°C.  $R_f$ : 0.68 (chloroform: methanol, 1:0.2).

**N-((1S)-Chloro(4-(oxiran-2-yl methoxy)phenyl)methyl)-N-(3-nitrophenyl) benzamide, 5f:** Yield 61.13%. Mol. Formula:  $\text{C}_{23}\text{H}_{19}\text{ClN}_2\text{O}_5$ . Mol. Wt. 438.86. m.p.90-92°C.  $R_f$ : 0.68 (chloroform: methanol, 1:0.2).

#### General procedure for the preparation of aryloxypropanolamine derivatives, 6a-f

Oxirane intermediate (0.01 mol, 1eq.) was dissolved in methanol (10 volume). To this solution was added isopropylamine/ tertiary butyl amine/ diethylamine/ piperidine (0.04 mol, 4 eq.) drop by drop with continuous stirring. The reaction mixture was refluxed at 80-90°C for 12-16 h as per requirement. Completion of the reaction was monitored by TLC. The excess of methanol was removed by distillation under reduced pressure to obtain the aryloxypropanolamine.

**N-((1S)-Chloro(4-(2-hydroxy-3-(isopropylamino)propoxy) phenyl)methyl)-N-phenylbenzamide, 6a:** Yield 42.5%. Mol. Formula:  $\text{C}_{26}\text{H}_{29}\text{ClN}_2\text{O}_3$ . Mol. Wt. 452.97. m.p.99-105°C.  $R_f$ : 0.48(chloroform: methanol, 1:0.2); IR (KBr): 3244 (-OH), 3045 (=C-H str., Ar.), 2946-2845 (C-H str.), 1670 (C=O str.), 1550 (C=C str., Ar.), 1100  $\text{cm}^{-1}$  (CN amine).

**N-((1S)-Chloro(4-(2-hydroxy-3-(piperidin-1-yl)propoxy)phenyl)methyl)-N-(4-chlorophenyl) benzamide, 6b:** Yield 48.73%. Mol. Formula:  $\text{C}_{28}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_3$ . Mol. Wt. 513.46. m.p.93-100°C.  $R_f$ : 0.42 (chloroform: methanol, 1:0.2); IR (KBr): 3104 (OH), 2942 (C-H str.), 1697 (C=O Str.), 1607-1560 (C=C str., Ar.), 1385 (C-N str.), 700  $\text{cm}^{-1}$  (C-Cl str.).

**N-((1S)-4-(3-(*tert*-Butylamino)-2-hydroxypropoxy)phenyl)chloromethyl)-N-(3,4-dichlorophenyl) benzamide, 6c:** Yield 30.43%. Mol. Formula:  $\text{C}_{27}\text{H}_{29}\text{Cl}_3\text{N}_2\text{O}_3$ . Mol. Wt. 535.89. m.p.80-85°C.  $R_f$ : 0.45(chloroform: methanol, 1:0.2); IR (KBr): 3046 (OH), 2950 (C-H str), 1681 (C=O str) 1590-1511 (C=C str. Ar.), 1410 (C-N str.), 750, 652  $\text{cm}^{-1}$  (C-Cl str.).

**N-((1S)-Chloro(4-(3-(diethylamino)-2-hydroxypropoxy) phenyl)methyl)-N-(o-tolyl) benzamide, 6d:** Yield 42.73%. Mol. Formula:  $C_{28}H_{33}ClN_2O_3$ . Mol. Wt. 481.03. m.p.91-96°C.  $R_f$ : 0.46 (chloroform: methanol, 1:0.2); IR (KBr): 3030 (OH), 2890 (C-H str), 1695 (C=O str) 1600, 1555-1520 (C=C str. Ar.),  $1365\text{ cm}^{-1}$  (C-N str.).

**N-((1S)-(4-(3-(tert-Butylamino)-2-hydroxypropoxy) phenyl)chloromethyl)-N-(3-methoxyphenyl) benzamide, 6e:** Yield 61.53%. Mol. Formula:  $C_{28}H_{33}ClN_2O_4$ . Mol. Wt. 497.03. m.p.174-179°C.  $R_f$ : 0.51 (chloroform: methanol, 1:0.2); IR (KBr): 3056 (O-H), 1514 (aromatic ring), 1676 (C=O), 2315 (C-N), 3400 (N-H),  $1139\text{ cm}^{-1}$  (C-N amine).

**N-((1R)-Chloro(4-(3-(diethylamino)-2-hydroxypropoxy)phenyl)methyl)-N-(3-nitrophenyl) benzamide, 6f:** Yield 33.62%. Mol. Formula:  $C_{27}H_{30}ClN_3O_5$ . Mol. Wt. 512.00. m.p.120-123°C.  $R_f$ : 0.47 (chloroform: methanol, 1:0.2); IR (KBr): 3062 (O-H), 2900 (C-H str.) 1692 (C=O, str.), 1594, 1505 (C=C str. Ar.),  $1411\text{ cm}^{-1}$  (C-N str.).

### Conclusions

A series of ten aryloxypropanolamine derivatives **6a** to **6j** were synthesized and evaluated for antihyperglycemic activity. Six compounds **6a** to **6j** have shown good antihyperglycemic activity. The compound **6c** is less active, **6a**, **6b** and **6d** show moderate activity, whereas **6e** and **6f** have shown good activity.

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