Available online on 15.06.2022 at ijmspr.com

International Journal of Medical Sciences and Pharma Research

Open Access to Medical and Research

Open Access **Research Article**

Synthesis, Characterization and Anti-Diabetic Activity of Novel 2-Substituted Indole Derivatives

Aman Singh Tomar[1]*, Neelam Khan[1], Neetesh Kumar Jain[2]

[1] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Oriental University Indore-India*

[2] *Department of Pharmacology, Faculty of Pharmacy, Oriental University Indore-India*

Article Info:

Article History:

Received 16 April 2022
Reviewed 29 May 2022
Accepted 10 June 2022
Published 15 June 2022

Cite this article as:

Tomar AS, Khan N, Jain NK, Synthesis, Characterization and Anti-Diabetic Activity of Novel 2-Substituted Indole Derivatives, International Journal of Medical Sciences & Pharma Research, 2022; 8(2):39-44

DOI: http://dx.doi.org/10.22270/ijmspr.v8i2.36

*Address for Correspondence:

Aman Singh Tomar, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Oriental University Indore-India

Email: at1422243@gmail.com

Abstract

Accordingly, the nitrogen in each nucleus, *viz.* 2-phenylindole, carbazole, phenothiazine and dibenzylamine, was planned to be alkylated applying several *N*-alkylating conditions, using either bromochloropropane or bromochlorobutane to give alkylated products with chloro-group available at the end of 2-carbon and 3-carbon chain. The chloro-group can then thought be utilized in reaction with *p*-hydroxyacetophenone to form ethereal linkage, by applying conditions of Williamson's ether synthesis. The acetyl group present in the products could then easily be converted into indole ring using conditions of Fischer's-indole synthesis.[57] Further, it was planned to confirm the structures of synthesized compounds using spectral and elemental analysis, apart from simple laboratory techniques like physical constants and classical chemical tests.

Keywords: Indole, 2-Phenylindole, Carbazole, Diabetes, Anti-diabetic activity.

INTRODUCTION:

A great deal of human health is affected by consumption of high-calorie diet and luxurious life style. Various evidences suggest that common health problem of modern society, *viz. diabetes mellitus*, obesity, cardiovascular diseases etc., are associated with intake of energy-rich food combined with decreased level of physical activity[1]. Recently, the World Health Organization (WHO) reported approximately 135 million people of the total world population to be affected by *diabetes mellitus*. The number has been predicted to rise up to 300 million by the year 2025[2]. The prevalence of *diabetes mellitus* in majority increases with age and obesity; over 20 % adults (≥ 60 years or older) have *diabetes*. At present more than 1 billion people are reportedly overweight; about 300 million people can be classified as obese[3, 4].Thus, *diabetes mellitus* can be a debilitating metabolic disorder that cumulates in a range of progressive secondary complications (discussed in following chapters). Time has now arrived for the sections of society concerned with the health and welfare to take some gigantic steps for curbing the widespread of this disorder so as to have a society with more percentage of people leading a better life[5].

Indole is aromatic benzo-fused heterocyclic containing nitrogen. The inclusion of lone pair electrons of nitrogen in the aromatic ring emphasize that indole is not a simple amine20. The heterocyclic compound is an important structural feature of many compounds, viz. amino acids, proteins, alkaloids, pigments etc20. Few NSAID, ibuprofen and indomethacin, have been reported to activate PPAR at micro-molar concentrations. Hence, in search of compounds without thiazolidinedione ring system, few teams reported compounds with indole ring replacing the previous heterocyclic system, as novel activators of PPAR[6].

MATERIALS AND METHODS:

Materials:

AR/LR grade reagents were used after purifying and drying.[29] TLC was performed using Silica gel G plates which were activated at 110˚C for 30 minutes, and developed using iodine vapors/UV light.[7] Solvent system used for TLC was a) *n*-hexane: toluene (4:1), b) toluene, c) chloroform, and d) ethyl acetate; R_f values of purified compounds are represented individually. Single spot TLC using various solvent systems ascertained purity of the compounds

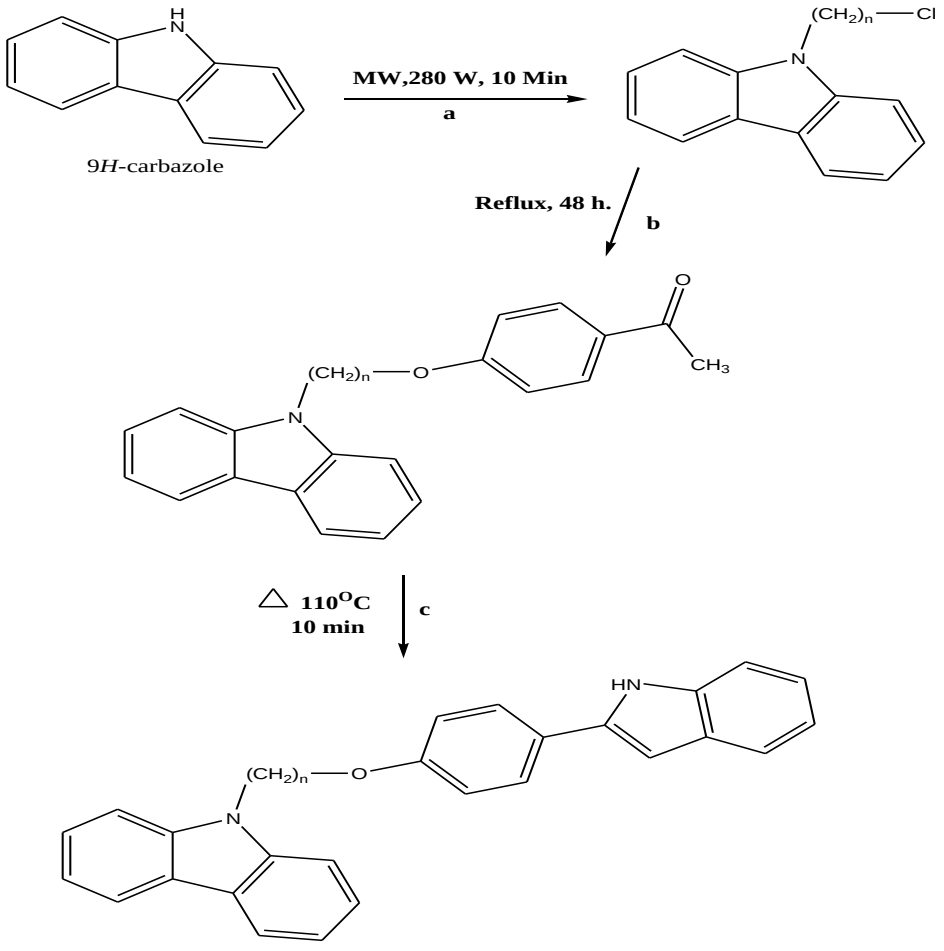
The compound, 2-phenylindole required in one of the schemes, was prepared in the laboratory, and its purity was ascertained by comparing its physical constant with the one reported in the literature. The solvents used for crystallization and the spectral characteristics of the products are mentioned along with their individual description. Three target compounds were obtained from the scheme of chemical reactions given in the preceding section.

***N*-alkylation**[8-10]**:** A mixture of nitrogen containing aromatic/heterocyclic compounds (0.1 mole), dihaloalkane (0.1 mole), tetrabutylammonium bromide (0.3 mole) and potassium hydroxide (0.1 mole) was placed in a microwave flask (100 mL). To this mixture, sufficient amount of dimethyl sulfoxide was added, and irradiated at 280 W for 10 minutes in a micro-wave oven. Subsequently, the reaction mixture was pored over of crushed-ice. The semi-solid mass that separated was extracted with dichloromethane, and chromatographed over silica gel for column chromatography (60-120).

Williamson's ether synthesis: *N*-alkylated product (0.1 mole) was mixed with 4-hydroxyacetophenone (0.1 mole) and potassium hydroxide (0.1 mole) in a round bottomed flask (100 mL). To this mixture, sufficient amount of acetone was added and stirred well; it was refluxed for 48 h. The reaction mixture was added over crushed ice[11]. The semi-solid mass that separated was extracted with dichloromethane, and chromatographed over silica gel for column chromatography (60-120).

Fischer's indole synthesis: Product from Williamson's ether synthesis (0.1 mole) was treated with drop-wise addition of phenyl hydrazine (0.1 mole), and the mixture was dissolved in rectified spirit. To this mixture, few drops of acetic acid were added. The reaction mixture was warmed for few minutes, and cooled immediately. The precipitate was separated, washed with cold rectified spirit, and transferred to 250 mL beaker containing polyphosphoric acid. The reaction mixture was heated on boiling water bath, stirred with thermometer maintaining the temperature at 110 ˚C for 10 minutes[12]. Ice-cold water was added to the reaction mixture, stirred well to complete the solution of polyphosphoric acid. The oily product which separated was extracted with ether, washed with cold water, and chromatographed over silica gel for column chromatography (60-120).

Synthetic scheme:



n= 3,4
a =1-Bromo 3-Chloropropane/1-Bromo 4-Chlorobutane,KOH,TBAB,DMSO
b = P-Hydroxyacetophenone, KOH, acetone
c = phenylhydrazine, polyphosphoric acid, acetic acid, ethanol

SYNTHETIC PROCEDURE:

Synthesis of 9-(3-Chloropropyl)-9*H*-carbazole (A i)

Carbazole (0.02 mole; 5 g), tetrabutylammonium bromide (0.06 mole, 19.33 g), and potassium hydroxide (0.02 mole, 1.12 g) were placed in mortar and triturated to mix completely. Then the reaction mixture was transferred to a microwave flask (100 mL). To this mixture, alkylating reagent 1-bromo-3-chlropropane (0.02 mole, 3.14 mL) was drop- wise added with stirring[13]. The general procedure described for ***N*-alkylation** was followed to get a white coloured oily compound, after chromatography (mobile phase *n*-hexane: toluene; 4:1). R_f = 0.4 (a)

Synthesis of 1-{4-[3-(9*H*-Carbazol-9-yl)propoxy]phenyl}ethanone (A ii)

A mixture of 9-(3-chloropropyl)-9*H*-carbazole (0.003 mole, 0.74 g), *p*-hydroxyacetophenone (0.003 mole, 0.5 g) and

potassium hydroxide (0.003 mole, 0.168 g) were placed in 100 mL round bottomed flask, and sufficient amount of acetone was added to this mixture. The general procedure described for **Williamson's ether synthesis** was followed[13]. After evaporating ether to dryness, the crude product was washed with 5% NaOH, and chromatographed over silica gel for column chromatography (60-120) with toluene.R_f = 0.61 (b)

Synthesis of 2-{4-[3-(9*H*-Carbazol-9yl)propoxy]phenyl}-1*H*-indole (A iii)

A mixture of 1-{4-[3-(9*H*-carbazol-9-yl)propoxy]phenyl}ethanone (0.002 mole, 0.8 g) and phenyl hydrazine (0.002 mole, 0.8 mL) were dissolved in warm rectified spirit. The procedure described for **Fischer-indole synthesis** was followed. The resulting mixture was extracted with ether. A greenish coloured semi-solid product was obtained.R_f = 0.59 (c)

Synthesis of 9-(4-Chlorobutyl)-9*H*-carbazole (B i)

Carbazole (0.02 mole; 5 g), tetrabutylammonium bromide (0.06 mole, 19.33 g), and potassium hydroxide (0.02 mole, 1.12 g) were placed in mortar and triturated to mix completely. Then the reaction mixture was transferred to a microwave flask (100 mL). To this mixture, alkylating reagent 1-bromo-4-chlorobutane (0.02 mole, 3.14 mL) was drop- wise added with stirring[14]. The general procedure described for ***N*-alkylation** was followed to get The oily product thus obtained was chromatographed using *n*-hexane: toluene (4:1). R_f = 0.71 (a)

Synthesis of 1-(4-(4-(9*H*-Carbazol-9-yl)butoxy)phenyl)ethanone (B ii)

A mixture of 9-(4-chlorobutyl)-9*H*-carbazole (0.001 mole, 0.31 g) *p*-hydroxyacetophenone (0.003 mole, 0.5 g) and potassium hydroxide (0.003 mole, 0.168 g) were placed in 100 mL round bottomed flask, and sufficient amount of acetone was added to this mixture. The general procedure described for **Williamson's ether synthesis** was followed. After evaporating ether to dryness, the crude product was washed with 5% NaOH, and chromatographed over silica gel for column chromatography (60-120) with toluene.R_f = 0.74 (b)

Synthesis of 9-(4-(4-(1*H*-indol-2-yl)phenoxy)butyl)-9H-carbazole (B iii)

A mixture of 1-(4-(4-(9*H*-Carbazol-9-yl)butoxy)phenyl)ethanone(0.0003 mole, 0.130 g) and phenyl hydrazine (0.002 mole, 0.8 mL) were dissolved in warm rectified spirit. The procedure described for **Fischer-indole synthesis** was followed[15]. The resulting mixture was extracted with ether. A greenish coloured semi-solid product was obtained. R_f = 0.69 (c)

Synthesis of 1-(3-Chloropropyl)-2-phenyl-1*H*-indole (C i)

2-phenyl-1*H*-indole (0.02 mole; 5 g), tetrabutylammonium bromide (0.06 mole, 19.33 g), and potassium hydroxide (0.02 mole, 1.12 g) were placed in mortar and triturated to mix completely. Then the reaction mixture was transferred to a microwave flask (100 mL). To this mixture, alkylating reagent 1-bromo-3-chlropropane (0.02 mole, 3.14 mL) was drop- wise added with stirring[16]. The general procedure described for ***N*-alkylation** was followed to get the product thus obtained was purified using column chromatography to obtain a white coloured oily product.R_f = 0.72 (d)

Synthesis of 1-{4-[3-(2-Phenyl-1*H*-indole)propoxy]phenyl}ethanone (C ii)

A mixture of 1-(3-chloropropyl)-2-phenyl-1*H*-indole (0.003 mole, 1.01 g)., *p*-hydroxyacetophenone (0.003 mole, 0.5 g) and potassium hydroxide (0.003 mole, 0.168 g) were placed in 100 mL round bottomed flask, and sufficient amount of acetone was added to this mixture. The general procedure described for **Williamson's ether synthesis** was followed. After evaporating ether to dryness[17], the crude product was washed with 5% NaOH, and chromatographed over silica gel for column chromatography with toluene. R_f = 0.67 (b)

Synthesis of 2-{4-[3-(2-Phenyl-1*H*-indole-1-yl)propoxy]phenyl-1*H*-indole

A mixture of 1-{4-[3-(2-phenyl-1*H*-indole)propoxy]phenyl}ethanone (0.003 mole, 1.24 g) and phenyl hydrazine (0.002 mole, 0.8 mL) were dissolved in warm rectified spirit. The procedure described for **Fischer-indole synthesis** was followed[18]. The resulting mixture was extracted with ether. The greenish product was obtained which was chromatographed using chloroform. The greenish product was obtained which was chromatographed using chloroform. R_f = 0.71 (c).

Table 1: data for Analysis of synthesize compound:

S.NO.	Compound code	Mol. Formula	Mol. Weight	% yield	Rf value
1.	Ai	$C_{15}H_{14}ClN$	243	89-90	0.4
2	Aii	$C_{23}H_{21}NO_2$	343	78-79	0.61
3	Aiii	$C_{29}H_{26}N_2O$	418	68-70	0.59
4	Bi	$C_{16}H_{16}ClN$	257	82-83	0.71
5	Bii	$C_{22}H_{21}NO_2$	331	62-63	0.74
6	Biii	$C_{30}H_{28}N_2O$	432	76-77	0.69
7	Ci	$C_{17}H_{16}ClN$	269	56-58	0.72
8	Cii	$C_{25}H_{23}NO_2$	369	63-65	0.67
9	Ciii	$C_{31}H_{28}N_2O$	444	45-46	0.71

Oral Glucose Tolerance Test:

Overnight fasted rats were anesthetized using anesthetic ether. Blood was withdrawn, from the *retro orbital plexus* situated in the eye-cavity of animals, twice at an interval of 30 min. After further 30 min, a glucose load (aqueous 50 % Dextrose) was orally fed to the animals corresponding to 2 g/Kg body weight. Blood was further withdrawn for subsequent 2 h, at an interval of 30 min[19-21].

The blood was subjected to centrifugation (2400 rpm, 10 min), serum separate and transfer to 96-was micro-titer plate, containing appropriate reagents, (as given below), and incubated for 10 min at 37 °C. The absorbance's of the solutions was read at 505 nm[22].

Table 2: Oral Glucose Tolerance Test

Solution	Blank	Standard	Test
Glucose Reagent	1.0 mL	1.0 mL	1.0 mL
Standard	- -	10 µL	- -
Sample	- -	- -	10 µl
Distilled Water	10 µl	- -	- -

The blood glucose levels present in the serum samples will calculate using the formula

Glucose (mg/dL) = $(A_T - A_B)/ (A_S - A_B)$ X 100

Where, A_T = Absorbance of test

A_S= Absorbance of standard

A_B = Absorbance of blank

The observe blood-glucose levels show in following table willexpress as mean ± S.E.M. The obtain data will analyses statistically by applying one-way ANOVA and *post hoc*Dunnet test, with $p< 0.05$ consider as significant.

RESULT AND DISCUSSION:

In an endeavor to develop compounds, to possess anti-hyperglycemic activity, containing the essential elements from structural-activity relationship of PPAR agonists, three target molecules were synthesized. Purity of the synthesized indole derivatives was assured by single spot TLC. The spectral data of the compounds satisfactorily supported the proposed structure. However, as imagined earlier, their elemental data could not be obtained, as the yields were too low. Also, for the same reason, ^{1}H-NMR and Mass data of the final compounds could be obtained.

The IR spectra of compounds support their structures. Apparently, spectrum **Ai** exhibits a strong peak at 1035 cm^{-1} due to C-N stretching indicating the presence of alkyl chain on the nitrogen, and at 673 cm^{-1} due to C-Cl stretching indicating the presence of chlorine group. Moreover, the peak at 3452.64 cm^{-1}- usually present in the spectrum of Carbazole due to N-H stretching – is not apparent here. IR spectrum **A ii** exhibits a strong peak at 1672 cm^{-1} due to the presence of C=O feature which isn't apparent in spectrum **A i** indicating the presence of ketonic group. The appearance of this peak at shorter wavelength indicates its aromatic character. Rest peak in the spectrum are similar to those in spectrum **A i**.

The spectrum **A iii** exhibits a peak at 3468.13 cm^{-1} due to N-H stretching; lamenting the formation of indole ring. The stretching due to C=O (1672 cm^{-1}, spectrum **A ii**), is not seen in the spectrum **A iii**. ^{1}H-NMR spectrum of compound **A iii** shows a δ values at 11.38 (1H: s, NH), 7.86- 7.01 (15H: m, aromatic protons), 6.98-6.71 (4H: m, aromatic protons), 4.09-4.06 (3H: m, NCH_2), 3.82-3.78 (3H: m, OCH_2), 2.20-2.15 (5H: m, CH_2). The mass spectrum of compound **A iii shows** M^+ peak at 416, which conforms the formation of designed compound.

IR spectrum **B i exhibits** a strong peak at 1055 cm^{-1} due to C-N stretching indicating the presence of alkyl chain on the nitrogen, and at 563 cm^{-1} due to C-Cl stretching indicates the presence of chlorine group. Moreover, the peak at 3452.64 cm^{-1}- usually present in the spectrum of Carbazole due to N-H stretching – is not apparent here. IR spectrum **B ii** exhibits a strong peak at 1705.13 cm^{-1} due to the presence of C=O feature which isn't apparent in spectrum **B i** indicating the presence of ketonic group. The appearance of this peak at shorter wavelength indicates its aromatic character. Rest of the peaks in the spectrum are similar to those in spectrum **B i**.

IR spectrum **B iii** exhibits a peak at 3444 cm^{-1}due to N-H stretching, lamenting the formation of indole ring. The stretching due to C=O (1705.13 cm^{-1}, spectrum **B ii**) is not seen in this spectrum. The ^{1}H-NMR spectrum of compound **B iii shows** δ values at 11.38 (1H: s, NH), 7.86- 7.01 (15H: m, CH), 6.98-6.71 (4H: m, aromatic protons), 4.35-4.23 (6H: m, N-CH_2-). The mass spectrum of compound **B iii** shows the M^+ peak at 402, which confirms the formation of designed compound**.**

IR spectrum **C i** exhibits a strong peak at 1074 cm^{-1} due to C-N stretching indicating the presence of alkyl chain on the nitrogen, and at 665 cm^{-1} due to C-Cl stretching indicating the presence of chlorine group. Moreover, the peak at 3468 cm^{-1}- usually present in the spectrum of 2-phenylindole due to N-H stretching – is not apparent here. IR spectrum **C ii** exhibits a strong peak at 1678 cm^{-1} due to the presence of C=O feature which isn't apparent in spectrum **C i,** indicating the presence of ketonic group. The appearance of this peak at shorter wavelength indicates its aromatic character. Rest of the peaks in the spectrum are similar to those in spectrum **C i**.

IR spectrum **C iii** exhibits a peak at 3421 cm^{-1}due to N-H stretching, lamenting the formation of indole ring. The stretching due to C=O (1678 cm^{-1}, spectrum **C ii**), is not seen here. The ^{1}H-NMR spectrum of compound **C iii shows** a δ values at 11.38 (1H: s, NH), 7.82- 7.01 (14H: m, aromatic protons), 6.98-6.74 (4H: m, aromatic protons), 4.09-4.06 (3H: m, NCH_2), 3.82-3.76 (3H: m, OCH_2), 2.14-2.07 (5H: m, CH_2). The mass spectrum of compound **C iii** shows M^+ peak at 416, which confirms the formation of designed compound.

Table 3: Data for Analysis of synthesize compound

S.NO.	Compound code	Mol. Formula	Mol. Weight	% yield	Rf value
1.	Ai	$C_{15}H_{14}ClN$	243	89-90	0.4
2	Aii	$C_{23}H_{21}NO_2$	343	78-79	0.61
3	Aiii	$C_{29}H_{26}N_2O$	418	68-70	0.59
4	Bi	$C_{16}H_{16}ClN$	257	82-83	0.71
5	Bii	$C_{22}H_{21}NO_2$	331	62-63	0.74
6	Biii	$C_{30}H_{28}N_2O$	432	76-77	0.69
7	Ci	$C_{17}H_{16}ClN$	269	56-58	0.72
8	Cii	$C_{25}H_{23}NO_2$	369	63-65	0.67
9	Ciii	$C_{31}H_{28}N_2O$	444	45-46	0.71

The popular experimental models -Alloxan-induced *diabetes* and Streptozotocin-induced *diabetes*- however, could not be used because in these models the induced *diabetes* is due to destruction of β-cells of *islet of Langerhans* in pancrease, therefore reducing the levels of circulating insulin leading to hyperglycemia. On the contrary, the synthesized compounds were to be tested against *Type 2 diabetes*. Moreover, attempts to induce *Type 2* diabetes in rats- dosing females with alcohol (36 % of body weight) during pregnancy and also during nursing- failed to induce the disorder in the off-springs, as was conclusive from the results of OGTT which was carried out when the animals were 16-weeks old. Hence, it became imperative to rely only on the results of OGTT carried on blood of normal animals. Based on the pharmacological studies carried out in our laboratory, *i.e.* OGTT, it can roughly be inferred that compound **B iii** effectively lowers the elevated blood-glucose levels; the effects shown is near to the effect exerted by the Pioglitazone and Rosiglitazone (seen below).

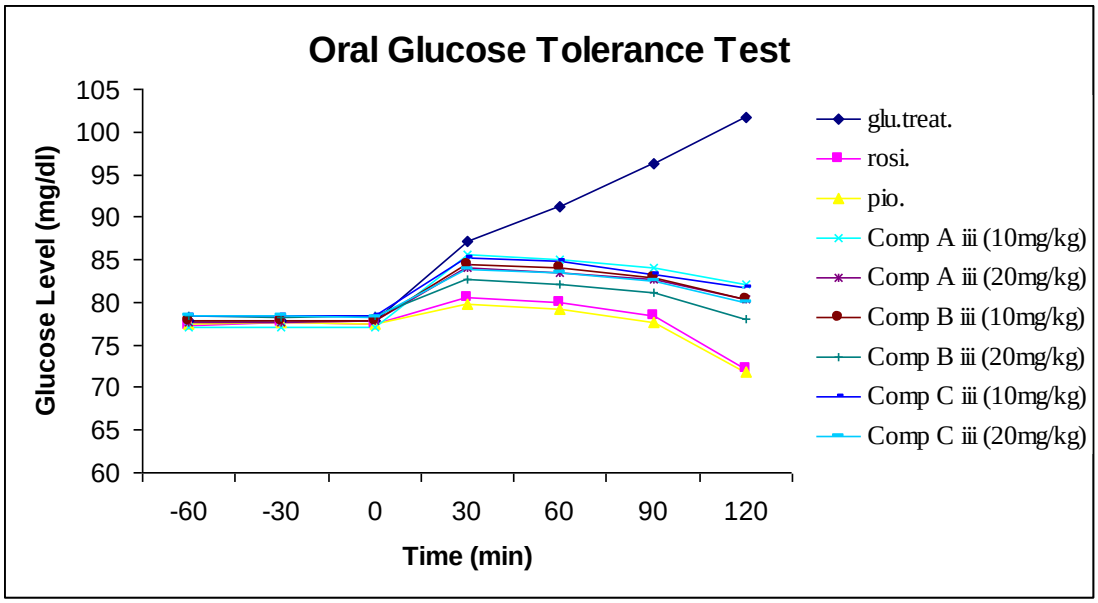


Figure 1: Oral glucose tolerance test

However, the true anti-hyperglycemic property of any of the synthesized compounds cannot be foreseen, the observed activity can only be used as an indication for further studies, as its anti-hyperglycemic potential was not evaluated using true animal model, nor its ability to bind with the concerned receptor was examined using *in vitro* assays, which become further scope of our research.

CONCULSION:

On the contrary, the synthesized compounds were supposed to be tested against *Type 2 diabetes*; the anti-hyperglycemic ability of synthesized compounds was envisaged to be established by their ability to increase sensitivity of peripheral tissues to circulating insulin in the animals. Hence, it was thought worth to validate and use a reported ethanol-induced diabetic model in rats, which would definitely examine the anti-hyperglycemic activity of the synthesized compounds, and also their anti-diabetic potential, especially for treating *Type 2 diabetes*.

REFERENCES:

1. Tripathi, K.D.; Essentials of Medical Pharmacology, 5th ed., Medical publisher 2004, 236

2. Alberti, K.G.M.M., Zimmet, P., Shaw, J.; Diabet. Med., 2007, 24:451-63 https://doi.org/10.1111/j.1464-5491.2007.02157.x

3. Mehana, A. S.; Am. J. Pharm. Educ., 2005; 69(5):1-12 https://doi.org/10.5688/aj690112

4. Elte, J.W. F., Blickle, J.F.; European Journal of Internal Medicine, 2012; 18:18-25 https://doi.org/10.1016/j.ejim.2006.09.007

5. Rangwala, S.M., Lazar, M.A.; Trends. Pharmacol. Sci., 2004; 25(6):331-36 https://doi.org/10.1016/j.tips.2004.03.012

6. Aurex, J.; Diabetologia, 1999, 42, 1033-49 https://doi.org/10.1007/s001250051268

7. Berger, J., Zhang, B., Moller, D.E.; et al. , Biochemistry and Molecular Biology, 1999; 274(10):6718-25 https://doi.org/10.1074/jbc.274.10.6718

8. Ferre, P.; Diabetes, 2014; 53:S43-S50 https://doi.org/10.2337/diabetes.53.2007.S43

9. Abraham, D.J.; Medicinal Chemistry Drug Discovery, 6th ed., Wiley Interscience, A John Wiley and Sons, 1998; 4:1-45

10. http:/en.wikipedia.org/wiki/indole

11. Henke, B.R., Adkison. K.K., Mook, R.R.; et al., Bioorg. Med. Chem. Lett., 1999; 9:3329-34 https://doi.org/10.1016/S0960-894X(99)00603-4

12. Dyer, J.R.; Applications of absorption spectroscopy of organic compounds, Prentice-Hall of India Private Limited, 2019, 84-85

13. Rybenzynski, P.J., Zeck, R.E., Burris, T.P.; et al., J. Med. Chem. , 2018; 47:196-209 https://doi.org/10.1021/jm0301888

14. Chenault, J., Cottineau, B., Toto, P.; et al., Bioorg. Med. Chem. Lett., 2021; 12:2105-08 https://doi.org/10.1016/S0960-894X(02)00380-3

15. Knutsen, L.J.S., Andersen, K.E., Nielsen, E.B.; et al., et al., J. Med. Chem. , 1993; 36:1716-25

16. Giannangeli, M., Cazzolla, N., Luparini, M.R.; et al., J. Med. Chem. , 1999; 42:336-45 https://doi.org/10.1021/jm970700n

17. U.S.Patent. 4, 450, 163 , May 22, 1984

18. Hamel, P, Girard, M.; J. Med. Chem. , 2020,65, 3123-25 https://doi.org/10.1021/jo9919207

19. Giles, P.R. Mark Rogers-Evans, M.R., Soukup, M.; et al., Organic Process Research & Development, 2020, 7, 2224

20. Zheng, M., Ye, D., Deng, Y.; et al., Bioorg. Med. Chem. Lett., 2017, 17, 2414-20

21. Aubry, C, Patel, A., Mahale, S.; et al., Tetrahedron. Lett. ,2015, 46, 1423-25 https://doi.org/10.1016/j.tetlet.2005.01.054

22. Chenault, J., Cottineau, B., Toto, P.; et al., Bioorg. Med. Chem. Lett., 2012, 12, 2105-2210 https://doi.org/10.1016/S0960-894X(02)00380-3