IJPSR (2022), Volume 13, Issue 9 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 January 2022; received in revised form, 25 March 2022; accepted, 26 April 2022; published 01 September 2022

SYNTHESIS OF 4- (4-SUBSTITUTED)-1-(3- SUBSTITUTED- 5, 6-DIHYDRO- [1, 2, 4] TRIAZOLO [3, 4-A] PHTHALAZIN-6-YLAMINO) AZETIDIN-2-ONE DERIVATIVES AS ANTIDIABETIC AGENTS

Smita Singh * and Pranjal Kumar Singh

S. R. M. Modinagar College of Pharmacy, SRM Institute of Science and Technology, Delhi NCR Campus, Delhi Meerut Road, Modinagar - 201204, Uttar Pradesh, India.

Keywords:

STZ-rat model, Roziglitazone, Triazolophthalazine, Antidiabetic activity, Phthalic anhydride

Correspondence to Author:
Ms. Smita Singh

S. R. M. Modinagar College of Pharmacy, SRM Institute of Science and Technology, Delhi NCR Campus, Delhi Meerut Road, Modinagar - 201204, Uttar Pradesh, India.

E-mail: smita0082@gmail.com

ABSTRACT: In this research work, numerous molecules that have substituted triazole phthalazine derivatives were obtained using phthalic anhydride as a starting material. It was taken as starting material that gave reaction in the precence of different conditions with different substituted benzoyl chloride that yielded 6 chloro-3 substituted 6a, 10 a-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazine derivatives (I-V). These intermediates further reacted with substituted benzaldehyde and yielded 4-2-3-Substituted - 6a, 10 a-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazin-6-yl) substituted hydrazinyl derivatives (VI-X) which were further react with triethyl amine and acetyl chloride yields (XXI-XXX). The antidiabetic effect was investigated using oral glucose tolerance test in normal and non-insulin-dependent diabetes mellitus (NIDDM) in STZ-rat model. In this model Roziglitazone taken as a standard drug for this pharmacological activity.

INTRODUCTION: Heterocyclic nitrogen-containing compounds have received great attention due to their various applications in different fields, especially as therapeutically active drugs. Examples of nitrogen heterocycles that have exciting biological properties are pyridazine and phthalazine derivatives. They constitute the structural profile for certain biologically active compounds and are thus known to be essential primary elements. Several studies have focused on the pharmacological benefits of derivatives of phthalazine derivatives and on a wide variety of contributions in different areas of interest.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(9).3543-49

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(9).3543-49

In organic chemistry, these structures are used extensively as intermediates for the synthesis of various compounds. In the other hand, derivatives of phthalazine as bioactive compounds have been thoroughly studied. They possess as prescribed extraordinary biological behaviour [1]. They are commonly known as flexible scaffolds for a range of pharmacological practises, such as analgesic, anti-inflammatory, antimicrobial, anti-depressant, diuretic, anti-hypertensive, anti-tuberculosis, and anti-HIV, as well as several other useful activities [2-4].

Phtalazines are the medicinally essential Versatile Pharmacophore and have drawn the interest of medicinal chemists due to their diverse pharmacological activities across the last decade. The basic functionalization of different ring locations makes them an appealing synthetic building block for new drug design and synthesis. A wide variety of pharmacological results arise

from the insertion of this versatile, biologically recognized pharmacophore into existing medicinally active molecules. A significant group of compounds is pyridazinones and phtalazines, many of which have widespread pharmacological properties such as antihypertensive, inhibitory platelet aggregation, and cardiotonic activities. Some are also well known for their use their marked analgesic, anti-inflammatory, antinociceptive and anti-ulcer activity. Phtalazines have also been identified currently as agents as antidiabetics, anticonvulsants, antiasthmatics, antimicrobials, *etc*. These positive studies suggest that the medicinal advantages of this enriched skeleton should be comprehensively studied [5]. Azoles, precisely 1,2,4-triazoles, are well known as well tolerated antidiabetic agents, displaying urease inhibition action [6-10]. In the continuation of our research work on the synthesis of various heterocyclic ring systems [11-14] the current study was conducted to establish new triazolophthalazine derivatives containing triazolophthalazine substitutions at 3rd and 6th positions and to examine their antidiabetic function. The target compounds **Fig. 1** were designed and synthesized and a comparative study of their antidiabetic activity were done using a rat model.

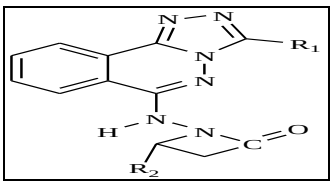


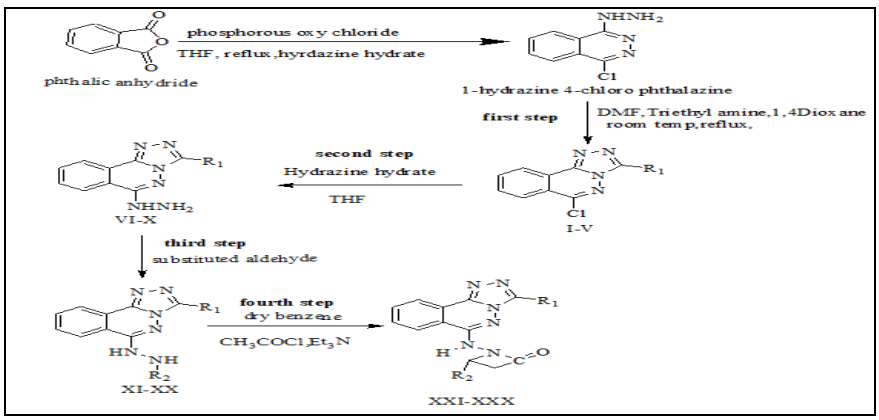
FIG. 1:

METHODS:

Source of Animals: The experiment was achieved using male Wistar albino rats (200-250 gm), housed in animal facilities that had free access to rat chow and water. The rats were kept under a controlled environment for about 1 week for adaptation and acclimatization before the experimental work was started. The procedures of this work were approved by the animal ethics committee of the Kalka Group of Institutions, Meerut (Regn.No.1902/PO/Re/S/16/CPCSEA) for animal experiments and animal taken from the Kalka Group of Institutions, Meerut (Regn.No.1902/PO/Re/S/16/CPCSEA) for animal experiments. Animal were owned by Kalka Group of Institutions, Meerut (Regn. No. 1902/PO/Re/S/16/CPCSEA). They are obtained from the Kalka Group of Institutions, Meerut (Regn.No.1902/PO/Re/S/16/CPCSEA) for animal activity. Concent letter number is Regn. No. 1902/PO/Re/S/16/CPCSEA. I released animals after experimental work. There is no use of euthanasia and anaes during the experimental procedure.

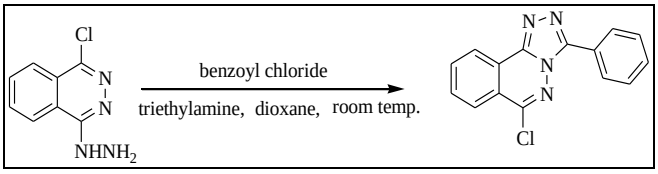
General Synthetic Procedure: The parent novel 4- (4-substituted)-1-(3- substituted- 5, 6-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazin-6-ylamino) azetidin-2-one derivatives (XXI-XXX) were obtained using a phthalic anhydride with dimethyl formamide, triethylamine and diaxane taken as reacting material for the synthesis of 1, 4 dichloro phthalazine. After this 1, 4 dichloro phthalazine reacts with substituted benzoyl chloride to give numbers of derivatives. These derivatives were further reacted phosphorus oxychloride and then with hydrazine hydrate to give the hydrazine derivatives. These derivatives are treated in dry benzene, triethylamine, and chloro acetyl chloride at low temperatures (below 5°C). (Scheme 1) [15-16].

Reaction Scheme 1-:

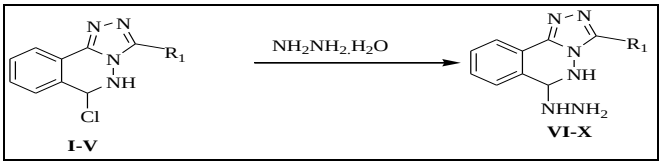


R_1: SUBSTITUTED BENZOYL CHLORIDE, R_2=SUBSTITUTED ALDEHYDE

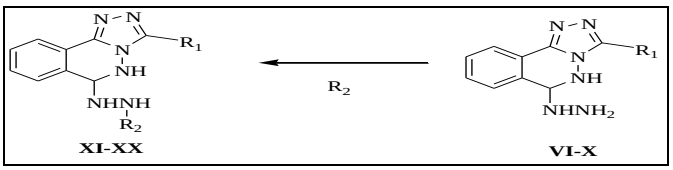
Step-1 Synthesis of 6 chloro -3-phenyl-[1, 2, 4] triazolo [3, 4-a] phthalazine: 4-hydrazine 1-chlorophthalazine (2gm), dioxin (20ml), Triethylamine (1.46mol) and benzoyl chloride (0.91 ml) mixed in round bottom flask (RBF). This reaction mixture was stirred for 2 h at room temperature on a magnetic stirrer. The reaction mixture was refluxed for 14 h at 50-55 °C, after completion of reaction precipitate was collected and recrystallized by methanol.



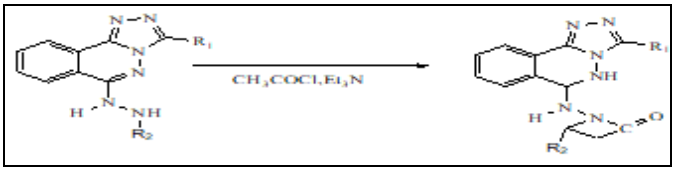
Step-2 Synthesis of 1-(3substituted- -[1, 2, 4] triazolo [3, 4-a] phthalazin-6yl) hydrazine: Previous step derivatives (6 chloro -3-phenyl-[1, 2, 4] triazolo [3, 4-a] phthalazine) taken (5 gm) and react with tetra hydro furan (THF) (60 ml) was added drop wise to a solution mixture of $NHNH_2.2H_2O$ (hydrazine hydrate) (6.28 gm) in tetra hydro furan (THF) 10 ml, at normal temp. Both reaction mixtures were stirred and heated at 60 °C for 60 min by magnetic stirrer. Then 50% of the organic solvent was evaporated under reduced pressure. Solution was treated with petroleum ether and kept it below 0 °C. Purity of compounds was checked by analytical spectrometry methods.



Step-3 Synthesis of 4-(2-(3-substituted [1, 2, 4] triazolo [3, 4-a] phthalazin-6-yl)hydrazinyl) substituted derivatives: Reaction mixture of VI (0.01 mol), with chloro benzaldehyde (0.01 mol) in equimolar amount in the presence of triethyl amine (12 ml) and acetyl chloride refluxed for 1 h. Reaction was monitored by TLC. At the end of process, the entire product was collected after filtration. Solid obtained was recrystallized with suitable solvent.



Step-4 Synthesis of 4-(-Substituted)-1-(3-phenyl-5, 6-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazine-6-yl amino) azetidin-2- one: Compounds was obtained from the previous step prepared were taken in solution 0.3 mol, in 30 ml of dry benzene added to stirred mixture of triethylamine 0.16 mol and acetyl chloride 0.16mol, at room temperature. The resulting materials were filtered and recrystallized with the proper ratio of solvent chloroform-methanol (1:1).



Experimental: The structures of the newly synthesized compounds were elucidated based on their IR, 1H-NMR, 13C-MR, MS spectral data and elemental analyses. The IR spectra of the obtained compounds exhibited the presence of 3020 (Ar-CH), 1635 (C=N), 1595(C=C), 1384(C-N); 662 1092(OCH_3) 1634 (-NH); 2983(-CH alkyl); 1726 (C=O); 1115(C-O). In addition to the expected aromatic protons signals, the 1H-NMR spectra revealed the appearance of new singlet for δ: 7.93, 7.85 (d, Ar-H, 2H), 7.48, 7.32, 7.22 (m, Ar-H, 4H), 7.38(d, Ar-H, 2-H); 8.14 (d, Ar-H, 2-H); 3.49.3.24 (d, C-H, 2-H), 4.7 (s, N-H, 1H). 13C-NMR spectra of the obtained compounds showed the appearance of new signals at range δ ^{13}C NMR: CH for benzene, (140, 136, 69,149, 120, 126, 127,128), C for triazole, (148,128), C for chain C (128, 129, 134, 173, 55). Moreover, the MS of compound 3g showed a molecular ion peak at m/z 424-511 (M+-1, 0.22%).

***In-vitro* Antidiabetic Study-**

Inhibition of α-amylase Enzyme: Starch solution (0.1%) was prepared by dissolving 0.1 g of starch in 100 mL of sodium acetate buffer (pH = 4.8, 16 mM). An enzyme solution was prepared by dissolving 27.5 mg of α-amylase in 100 mL of deionized H_2O. A colorimetric reagent was prepared by dissolving 1 g of 3,5-dinitro salicylic acid in deionized H_2O (20 mL) and 0.16 g sodium hydroxide (in 10 mL deionized H_2O) and 4 g of sodium potassium tartrate was added gradually to the mixture. The mixture was mixed well and the volume was made up to 100mL using deionized H_2O. Both control (100 µL) and the sulfonylurea or

TZD derivatives (100 µL) were separately mixed with the starch solution (100 µL) and left for 30 minutes to react with the α-amylase solution (under alkaline conditions at 25°C).

The action was recorded after 5 min. The liberated maltose was measured quantitatively by the reduction of 3,5-dinitro salicylic acid to 3-amino-5-nitrosalicylic acid. This reaction was measured at 540 nm [17, 18, 19].

***In-vivo* Antidiabetic Study:**

Animals: The experiment was achieved using male Wistar albino rats (200-250 g), housed in animal facilities that had free access to rat chow and water. The rats were kept under a controlled environment for about 1 week for adaptation and acclimatization before the experimental work was started. The animal ethics committee approved the procedures of this work of the Kalka Group of Institutions, Meerut (Regn. No. 1902/PO/Re/S/16/CPCSEA) for animal experiments.

Dose Determination: Rosiglitazone was applied as a standard antidiabetic drug at a 4 mg/kg dose in 1% Arabic gum and was administered orally [20]. Equivalent weights of the tested compounds were used since it is critical to determine the suitable dose for each compound at equivalent doses basis.

Sucrose-loaded model: The male Wistar rats were fasted overnight. Blood was collected, and then the test triazolophthalazine derivatives were given to the corresponding groups (each group consists of 3 rats) orally.

A sucrose load of (10 g/ kg) body weight was given to each rat after 30 minutes post-treatment. Blood samples were collected after 30, 60, 90 and 120 min from the sucrose treatment. The percentage (%) reduction in blood glucose level was determined according to the AUC protocol [21].

Streptozotocin-induced Diabetes: Male Wistar rats were fasted overnight and were injected intraperitoneally with streptozotocin (STZ, 65 mg/kg body weight) dissolved in a citrate buffer (pH 4.5, 50 mM). These rats were given access to a sucrose solution (15 g/100 mL) to prevent hypoglycemia. STZ was purchased from (Sigma-Aldrich, Co., St. Louis, USA. Catalog number: 1001062761) [22, 23].

Experimental Design: Twenty rats (four groups of 5 rats each, n = 5) were used to investigate the antihyperglycemic effect of triazolophthalazine derivatives. Group 1 was the control untreated group; Group 2 was a diabetic control group; Group 3 was treated with the reference antidiabetic drug (rosigilitazone, 100 mg/Kg). Group 4 was given the various triazolophthalazine derivatives (XI-XX, 100 mg/Kg). The treated groups administered the rosigilitazone and the different derivatives orally.

METHODS: For each group, blood glucose was determined at 0, 1, 2, 4, and 6 hours after the oral administration of compounds using a glucometer (Kalka Group of Institutions, Meerut), and the obtained results are shown in Table I.Values were expressed as mean± SEM. Compared with the Barferoni ANOVA test, data was evaluated by measurement of variance as well as group means.

Effects of Triazolophthalazine Derivatives on Fasting Blood Glucose Levels: During the experiment, fasting blood glucose levels in normal and diabetic control rats remain unchanged. However, the blood glucose levels were increased significantly in the case of untreated rats compared with the normal control. In contrast, a drop in the high blood glucose levels was observed in the diabetic rats when treated with compounds XXII, XXV, XXVII, and XXX rosiglitazone. By the completion of the experiment (after 4 weeks), 100 mg/Kg dose of compound XXV reduced the level of blood glucose by 49.2%, whereas the rosiglitazone treatment decreased the blood glucose levels by 54.4%. Furthermore, no significant blood glucose-lowering effect was observed for compounds XXI, XXIII, XXIV, XXVI, XXVIII and XXIX.

RESULT & DISCUSSION: The structures of the newly synthesized compounds were elucidated based on their IR, 1H-NMR, 13C-MR, MS spectral data, and elemental analyses. The IR spectra of the obtained compounds exhibited the presence of 3020 (Ar-CH), 1635 (C=N), 1595(C=C), 1384(C-N); 662 1092(OCH3) 1634 (-NH); 2983(-CH alkyl); 1726 (C=O); 1115(C-O). In addition to the expected aromatic protons signals, the 1H-NMR spectra revealed the appearance of new singlet for δ: 7.93, 7.85 (d, Ar-H, 2H), 7.48, 7.32, 7.22 (m, Ar-

H, 4H), 7.38(d, Ar-H, 2-H); 8.14 (d, Ar-H, 2-H); 3.49.3.24 (d, C-H, 2-H), 4.7 (s, N-H, 1H). 13C-NMR spectra of the obtained compounds showed the appearance of new signals at range δ 13C NMR: CH for benzene, (140, 136, 69,149, 120, 126, 127,128), C for triazole, (148,128), C for chain C (128, 129, 134, 173, 55). Moreover, the MS of compound XXV showed a molecular ion peak at m/z 424-511 (M+-1, 0.22%). The synthesized triazolophthalazine derivatives showed significant activity (80.0%, 76.56%, and 75.43%) against α-amylase enzyme at different concentrations. The results of the experimental works are summarized in **Table 1** and **Fig. 2.**

TABLE 1: PHYSICOCHEMICAL PARAMETER OF COMPOUNDS4- (4-SUBSTITUTED)-1-(3- SUBSTITUTED- 5, 6-DIHYDRO- [1, 2, 4] TRIAZOLO [3, 4-A] PHTHALAZIN-6-YLAMINO) AZETIDIN-2-ONE DERIVATIVES. (XXI-XXX)

Compound code	R_1	R_2	R_f Value	M.P.(°C)	% Yield	Mol. Formula	Mol. Weight
XXI	Benzoyl chloride	4-Nitro benzaldehyde	0.69	130-132	72	$C_{24}H_{19}N_7O_3$	453
XXII	4-Methoxy Benzoyl Chloride	4-Nitro benzaldehyde	0.73	140-142	76	$C_{25}H_{21}N_7O_4$	483
XXIII	4-Chloro Benzoyl Chloride	4-Nitro benzaldehyde	0.66	126-128	65	$C_{24}H_{18}ClN_7O_3$	487
XXIV	4-Fluoro Benzoyl Chloride	4-Nitro benzaldehyde	0.80	136-138	67	$C_{24}H_{18}FN_7O_3$	471
XXV	4-Acetoxy Benzoyl Chloride	4-Nitro benzaldehyde	0.75	140-142	74	$C_{26}H_{21}N_7O_5$	511
XXVI	Benzoyl chloride	4-Hydroxy Benzaldehyde	0.77	120-122	54	$C_{24}H_{20}N_6O_2$	424
XXVII	4-Methoxy Benzoyl Chloride	4-Hydroxy Benzaldehyde	0.63	112-114	71	$C_{26}H_{22}N_6O_4$	454
XXVIII	4-Chloro Benzoyl Chloride	4-Hydroxy Benzaldehyde	0.67	118-120	65	$C_{24}H_{19}ClN_6O_4$	458
XXIX	4-Fluoro Benzoyl Chloride	4-Hydroxy Benzaldehyde	0.73	136-138	67	$C_{24}H_{19}FN_6O_2$	442
XXX	4-Acetoxy Benzoyl Chloride	4-Hydroxy Benzaldehyde	0.64	122-124	74	$C_{26}H_{22}N_6O_4$	482

Note: Solvents system: ethyyl acetate: chloroform

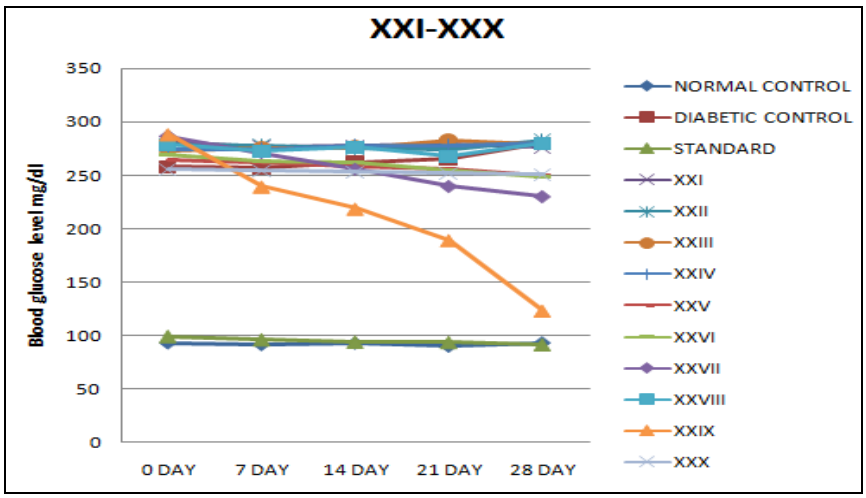


FIG. 2: EFFECT OF SYNTHETIC COMPOUNDS (XXI-XXX) ON BLOOD GLUCOSE LEVEL OF RAT

The synthesized triazolophthalazine derivatives showed a significant reduction in blood glucose level in the Sucrose-loaded model.

No significant blood glucose-lowering effect was observed for compounds XXII, XXV, XXVII and XXX **Table 2.**

TABLE 2: EFFECT OF ROSIGLITAZONE AND THE SELECTED 4-(-SUBSTITUTED)-1-(3-PHENYL-5, 6-DIHYDRO-[1, 2, 4] TRIAZOLO [3, 4-A] PHTHALAZINE-6-YL AMINO) AZETIDIN-2- ONE DERIVATIVE (XXI-XXX) ON FASTING BLOOD GLUCOSE LEVELS OF NORMAL DIABETIC AND TREATED RATS

Groups	Blood glucose level(mg/dl)				
	0 day	7day	14 day	21 day	28 day
Normal control	93.23 ± 2.80	91.72 ± 2.69	93.01 ± 1.82	90.18 ± 2.79	93.37 ± 2.65
Diabetic control	258.38 ± 2.1	257.19 ± 5.7	262.31 ± 2.3	265.12 ± 2.88	279.64 ± 2.89
Std.	99.23±3.52	96.22 ± 1.51	94.17±0.98	93.84 ±2.30	91.71±1.09
XXI	286.68±2.84	279.35±2.00	277.98±1.71	275.14±3.11	267.66±3.65
XXII**	280.01±3.63**	246.35±1.36**	222.98±3.75**	198.30±2.22**	151.99±2.03**
XXIII	257.18±2.77	250.35±2.02	255.14±1.88	248.64±2.68	241.41±1.66
XXIV	265.01±1.79	264.52±2.41	259.31±2.39	251.14±3.21	243.32±2.07
XXV**	280.51±2.77**	254.68±0.97**	235.64±2.59**	186.64±2.66**	142±2.718**
XXVI	274.34±2.54	258.18±2.23	262.81±1.87	262.14±2.679	255.99±1.77
XXVII**	273.34±1.55**	257.85±4.65**	240.64±2.14**	195.64±3.13**	156.99±2.88**
XXVIII	269.51±1.59	269.18±1.99	273.98±2.30	268.97±2.43	263.99±2.69
XXIX	265.68±1.72	268.02±3.26	271.64±1.72	269.30±2.70	267.66±1.39
XXX**	280.18±2.96**	247.52±1.76**	213.98±3.77**	199.14±2.35**	159.49±1.87**

Note: All determinations were carried out in a triplicate manner and values are expressed as the mean ± SD. Values are expressed as mean ± SEM (n=6),*** p<0.001,**p<0.01, *p<0.05, compare to diabetic control, Rosiglitazone was used as standard drug.

DISCUSSION: In this research work, numerous molecules that have substituted triazole phthalazine derivatives were obtained by using 4-hydrazine-1 chlorophthalazine as reacting molecule and different substituted benzoyl chloride that yielded 6 chloro-3 substituted 6a,10 a-dihydro-[1, 2, 4] triaolo [3, 4-a] phthalazine derivatives (I-V). These intermediates were treated with hydrazine hydrate to yield 6 hydrazine-3 substituted 6a, 10a-dihydro-[1, 2, 4] triaolo [3, 4-a] phthalazine derivatives (VI-X). These intermediates further reacted with substituted benzaldehyde and yielded 4-2-3-Substituted-6a, 10 a-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazin-6-yl) substituted hydrazinyl derivatives (XI-XX). These intermediate further treated with thioglycollic acid and yielded (XXI-XXX). 4-2-3-Substituted-6a, 10 a-dihydro-[1, 2, 4] triazolo [3, 4-a] phthalazin-6-yl) substituted hydrazinyl derivatives (XXI-XXX). Structures of all synthesized molecules were confirmed by using IR, ^{1}HNMR, MASS and elemental analysis spectroscopic techniques.

Antidiabetic Activity: All the synthesized compounds were screened *in-vivo* for their antidiabetic activity by a streptozotocin-induced diabetic model in albino rats. From the series XXII**, XXV**, XVII**, XXX**only some compounds had shown a significant reduction in blood glucose as compared to control diabetic rats. Those compounds having electron-donating substituents, i.e. XXII**, XXV**, XXVII** and XXX**, showed a significant increase in antidiabetic activity. it was interesting to note that compound XVIII, XIX, XXIX, having both electron donating at different position and electron with drawing group at different position of the phenyl ring showed increase in antidiabetic activity.

ACKNOWLEDGEMENT: Authors are grateful to Prof. Ranjeet Singh, Director of Pharmacy Department (Shobhit University), and Prof. Vijay Kumar Sharma, Director of Pharmacy Department (K.N. ModiInstitute of Pharmaceutical Education and Research) for supporting and motivating of completion of my research work.

CONFLICTS OF INTEREST: This research work does not have any conflict of interest because all work is done by me individual work all funding resources are self-funding by me.

REFERENCES:

1. Nahed F, Ghaffar AE, Mona A and Ghanem HM: Synthesized and biochemical evaluation of some substituted phthalazines. J Am Sci 2011; 7: 4771-781.
2. Mohammad A: Mini review on importance of pyridazinone and phthalazine moiety in medicinal chemistry with scaffold of pharmacological activities. International Journal of Pharmaceutical Chemistry 2015: 5:12. https://doi:10.7439/ijpc. www.ssjournals.com.
3. Asif M: Some recent approaches of biologically active substituted pyridazine and phthalazine drugs. Curr Med Chem 2012; 19: 18 2984–2991. DOI: 10.2174/092986712800672139

4. Asif M. Singh A and Siddiqui A: The effect of pyridazine compounds on the cardiovascular system. Med Chem Res 2012; 21: 3336-3346.
5. Seth S, Sharma A and Raj D: Pyridazinones: a wonder nucleus with scaffold of pharmacological activities. Am J Biol & Pharm Res 2014; 3: 105-116.
6. Mohamed AA Mounir, Abd Allah A and Myma El-Saghier MM: Synthesis and antidiabetic activity of novel triazole derivatives containing amino acids. J Heterocyclic Chem 2020; 57: 2365–2378.
7. Ibrar A, Khan I and Abbas N: Triazolothiadiazines as a new class of efficient DNA intercalating agents. Arch. Pharm.Chem. Life Sci 2013; 346: 423.
8. Mentese MY, Bayrak H, Uygun Y, Mermer A, Ulker S, Karaoglu SA and Demirbas N: Microwave assisted synthesis of some hybrid molecules derived from norfloxacin and investigation of their biological activities. Eur J Med Chem 2013; 67: 230. https://doi.org/10.1016/j.ejmech.2013.06.045.
9. Khan I, Ali S, Hameed S, Rama NH, Hussain MT, Wadood A, Uddin R, Haq ZU and Khan A: Eur J Med Chem 2010; 45: 11 5200. https :// doi.org/10.1016/j.ejmech.2010.08.034.
10. Bekircan O and Ozdemir Y: Synthesis and evaluation of lipase inhibitory activities of substituted 1, 2 ,4-triazole derivatives. Indian Journal of Chemistry 2020; 59: 1409-1417.
11. Murphy GJ and Holder JC: PPAR-Gamma Agonists: Therapeutic Role in Diabetes, Inflammation and Cancer. Trends Pharmacol Sci 2000; 21(12): 469-474.
12. Aboudi J, Bayat Y, Abedi Y, Nabati M and Mahkam M: 3-Nitro, 1-Amino Guanidine and 5-Hydrazino-1H-Tetrazole Derivatives as New Energetic Materials. J Chem Chem Eng 2015; 34(2): 1.
13. Behmadi H, Moghaddam ZA, Poormorteza N and Beyramabadi: New Strategy for the Synthesis of Morpholine Cores: Synthesis from N-Propargylamines. J Chem Chem Eng 2017; 36(1): 11.
14. Hasaninejad A, Zare A, Zolfigol M A, Abdeshah M, Ghaderi A and Nami-Ana F: Synthesis of Poly-Substituted Quinolines *via* Friedländer Hetero-Annulation Reaction Using Silica-Supported P2O5 under Solvent-Free Conditions. Iran J Chem Chem Eng 2011; 30(1); 73.
15. Sun XY, Chuan Hua, Deng X Q, Wei CX, Sun ZG and Quan ZS: Synthesis and anti-inflammatory activity evaluation of some novel 6-alkoxy (phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives. European Journal of Medicinal Chemistry 2010: 45; 4807-4812.
16. Carling RW, Moore KW, Street LJ, Wild D, Isted, C, Leeson PD, Thomas S, O'Connor, D, McKernan, RM, Quirk K, Cook SM and Atack J: R: 3-Phenyl-6-(2-pyridyl) methyloxy-1, 2, 4-triazolo[3, 4-a] phthalazine and analogues high- affinity y-Aminobuteric acid-A Benzodiazepine receptors ligands with a2, a3 and a5-subtype binding selectivity over a1. J Med Chem 2004: 47; 1807.
17. Beyzaei H, Beygi A and Aryan R: One-pot Synthesis and Characterization of Highly Functionalized Thiazoles. Iran J Chem Chem Eng 2016; 35(4); 31.
18. Malik CP and Singh MB: Plant Enzymology and Histoenzymology, Kalyani Publishers New Delhi 1980; 278.
19. Mowla A, Alauddin M, Rahman MA, Ahmed K and Tradit J: Comparative analysis of chemical and phytochemical compositions of four selected medicinal plants and evaluation of antidiabetic properties of aqueous extracts of trigonella foenum-graecum and combination of trigonella foenum-graecum - momordica charantia. International Journal of Pharmaceutical Sciences and Research 2009: 6(3); 255.
20. Singh FV, Parihar AS, Chaurasia S, Singh AB, Singh SP, Tamrakar AK and Srivastava A: 5,6-Diarylanthranilo-1,3-dinitriles as a new class of antihyperglycemic agents. Bioorg Med Chem Lett 2009: 19 (8); 2158. https://doi.org/10.1016/j. bmcl.2009.02.118.
21. Kim NN, Stankovic MTT, Cushman I. Goldstein R and Traish AM: Streptozotocin-induced diabetes in the rat is associated with changes in vaginal hemodynamics, morphology and biochemical markers. BMC Physiol 2006; 6(4). https://doi. org/10.1186/1472-6793-6-4.
22. Qinna NA and Badwan AA: Impact of streptozotocin on altering normal glucose homeostasis during insulin testing in diabetic rats compared to normoglycemic rats Drug Des. Dev Ther 2015; 9: 2515. DOI https://doi.org/10.2147/DDDT.S79885

How to cite this article:
Singh S and Singh PK: Synthesis of 4- (4-substituted)-1-(3- substituted- 5, 6-dihydro- [1, 2, 4] triazolo [3, 4-a] phthalazin-6-ylamino) azetidin-2-one derivatives as antidiabetic agents. Int J Pharm Sci & Res 2022; 13(9): 3543-49. doi: 10.13040/IJPSR.0975-8232.13(9).3543-49.