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DOCKING, SYNTHESIS AND EVALUATION OF NOVEL DERIVATIVES OF SUBSTITUTED CHALCONES AS ANTIHYPERGLYCEMIC AGENTS

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ABSTRACT

Various substituted chalcone derivatives (4A-4E) were synthesized. The structures of these compounds were established by spectral (IR, ^{1}H-NMR, Mass) analysis. The synthesized compounds were screened for their antihyperglycemic activity. Compound 4-C (2-(3-(4-methoxyphenyl)-1H-pyrazol-5-yl) phenol) was found to possess potent antihyperglycemic activity.

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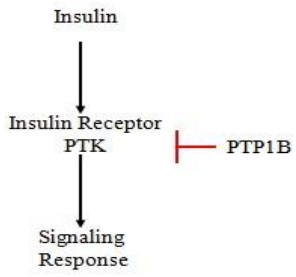
INTRODUCTION:

Diabetes mellitus (DM) is a heterogeneous metabolic disorder that is characterized by high levels of blood glucose with disturbances of carbohydrate, lipid, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Various heterocyclic derivatives of substituted chalcone compounds possess différent biological activities such as Protein Tyrosine Phosphatases (PTP)-1B inhibitory, antifungal, anti-inflammatory, anticonvulsant, antitubercular and immunomodulatory activity. The deregulation of PTP activity contributes to the pathogenesis of several human diseases, including cancer, diabetes, and immune disorders[1–3]. PTP1B plays an important role in down-regulating insulin signaling cascades via tyrosine dephosphorylation of the insulin receptor, which renders it inactive, or dephosphorylation of insulin receptor substrates 1 and 2, which inhibits their interactions with downstream signaling molecules (Figure 1) [2-4]. The present investigation involves docking, synthesis and evaluation of novel derivatives of substituted chalcone *via* cyclization of substituted chalcone and their screening for antihyperglycemic activity.



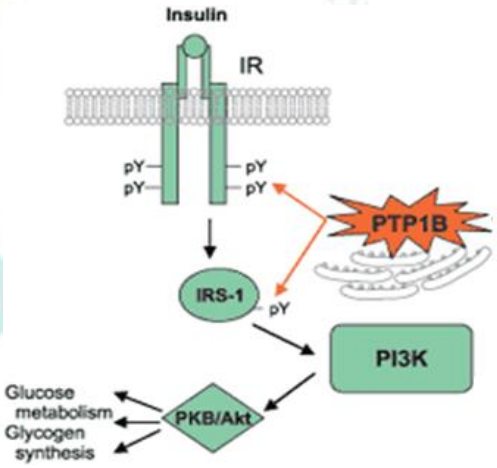


Figure 1: Role of PTP1B in hyperglycemia.

MATERIALS AND METHODS:

Melting points were determined on a capillary melting point apparatus (Lab Hosp). IR spectra were determined with a Thermo-Electron FT-IR spectrophotometer within range 400-4000 cm^{-1}. ^{1}H NMR spectra were recorded on a Bruker's AVANCE-III 400MHz FT NMR spectrometers. The mass spectra were measured on a Bruker microTOF QII mass spectrometer coupled to waters acquity LC system.

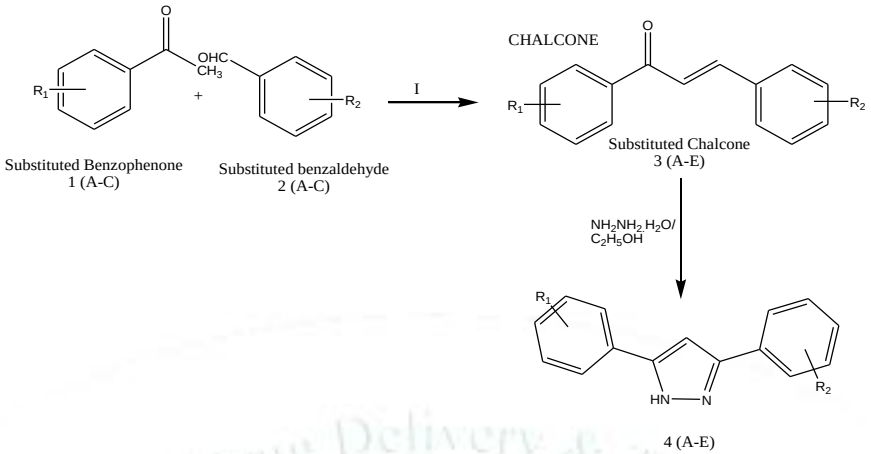
General Procedure for Synthesis of Substituted Chalcones: 3 (A-E)

A solution of sodium hydroxide (30%) in water and rectified spirit (100 mL) was continuously stirred in mechanical stirrer under ice cooled condition. Substituted acetophenone (0.015 mol) followed by

substituted benzaldehydes (0.025 mol) was continuously added. The mixture stirred until it became thick enough (Approx. 6 hr). The reaction mixture was kept at 8°C overnight. The product was filtered and recrystallized from ethanol.

General Procedure for Synthesis of Heterocyclic Derivatives of Substituted Chalcones: 4 (A-E)

A mixture of substituted Chalcones 4 (A-E) (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) in ethanol (50 mL) was refluxed for 6 hrs on a water bath followed with addition of ice cold water at room temperature. The mixture was kept overnight at 8°C. The precipitates were filtered, washed with distilled water and dried. The product was recrystallized with ethanol to obtain the final product 4 (A-E).



Scheme 1: Synthesis of proposed compounds.

Table 1: Details of synthesized compounds

S. No.	Compound code	R1	R2
1.	4A	4-OH	4-OMe
2.	4B	3-OH	4-OMe
3.	4C	2-OH	4-OMe
4.	4D	4-OH	3,4-Dimethoxy
5.	4E	4-OH	3,4-Methylenedioxy

Table 2: Spectral analysis of the synthesized compounds

Compound code	Mol. formula	Mol. weight	M.P. (ºC)*	IR spectra (cm^{-1})	Mass Spectra (Molecular ion peak)	^{1}H NMR Spectra (δ) in ppm
4 A	$C_{16}H_{14}N_2O_2$	266.29	170-175ºC	3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3022 (C-H str. aliphatic), 1522 (C=C str.), 1420 (C=N str. aromatic), 820 (C-H bend, aromatic).	268	7.5 (r, 4H, aromatic ring), 6.7-7.37 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87-3.7 (s, OCH3), 13.7 (r, NH).
4 B	$C_{16}H_{14}N_2O_2$	266.29	160-165ºC	3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3025 (C-H str. aliphatic), 1690 (C=C str.), 1425 (C=N str. aromatic), 901 (C-H bend).	268	7.6 (r, 4H, aromatic ring), 6.8-7.37 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 2.87-3.7 (s, OCH3), 13.7 (r, NH).
4 C	$C_{16}H_{14}N_2O_2$	266.29	161-166ºC	3246 (O-H str.), 3236 (aromatic N-H str.), 3229 (C-H str.), 3025 (C-H str. aromatic), 1416 (C=N str.	267.80	7.6 (r, 4H, aromatic ring), 6.79-7.37(m, 4CH, aromatic ring), 5.0(d, COH

				aromatic), 1352 (C=C str.), 910 (C-H bend).		aromatic), 2.87-3.7(s, OCH3), 13.7 (r, NH).
4 D	$C_{17}H_{16}N_2O_3$	296.32	180-185ºC	3082 (O-H str.), 3232 (aromatic C-H str.), 1609 (N-H bend), 1520 (C=C str.), 1120 (C-O-C str. asymmetric), 910 (C-H bend), 876 (C-H bend).	294.12	7.6 (r, 4H, aromatic ring), 6.79-7.31 (m, 4CH, aromatic ring), 5.0(d, COH aromatic), 2.87-3.7 (s, 2OCH3), 13.7 (r, NH).
4 E	$C_{16}H_{12}N_2O_3$	280.28	166-171ºC	3082 (O-H str.), 3232 (aromatic C-H str.), 1609(N-H bend), 1520 (C=C str.), 1495 (C-O-C str. asymmetric), 947(C-H bend), 875 (C-H bend).	282.11	7.6 (r, 4H, aromatic ring), 6.79-7.31 (m, 4CH, aromatic ring), 5.0 (d, COH aromatic), 5.9 (d, CH2 in ring), 13.7 (r, NH).

*uncorrected

Biological Activity:

All the synthesized compounds 4 (A-E) were screened for their antihyperglycemic activities by Sucrose Loaded Diabetic model using albino mice. Fasting blood glucose level of each animal was checked by glucometer using glucostrips (ACCU-CHEK) after 16 h starvation. Animals showing blood glucose level between 60 to 80 mg/dl at 0 min were finally selected and divided into groups of five animals in each. Mice of experimental group were administered the suspension of the test sample orally prepared in 0.1 % CMC at desired dose levels i.e. 100 mg/kg body weight of compounds and standard antidiabetic drug i.e. glibenclamide. Animals of control group were given an equal amount of 0.1 % CMC. An oral sucrose load of 10 g/kg body weight was always given to each animal exactly after 30 min post administration of the test sample/ vehicle. Blood glucose profile of each mice was again determined at 30, 60, 90 and 120 min post administration of sucrose.

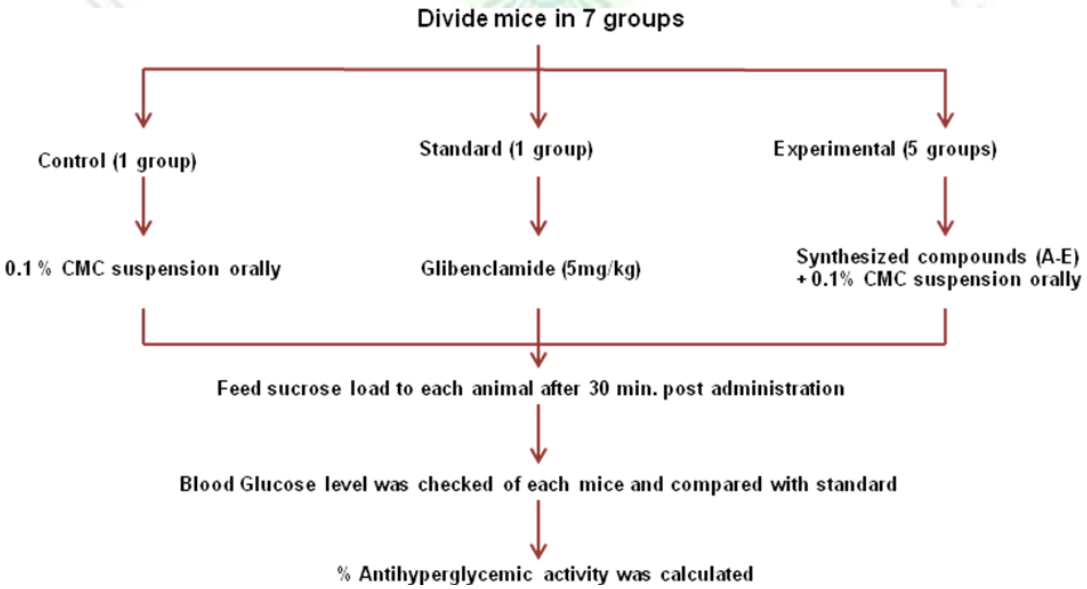


Figure 2: Flow chart for antihyperglycemic activity using "Sucrose Loaded Diabetic Model"

Molecular docking

The protein structure (PDB ID: 2QBP) downloaded from protein data bank was used without any modification. In view of biological activity of pyrrazoles the potential of some substituted Pyrrazoles for PTP-1B inhibition was studied using molecular docking. Some of the designed compounds were docked in the active site of PTP-1B using Python prescription (PyRx). Among these compounds 4-C (2-(3-(4-methoxyphenyl)-1H-pyrazol-5-yl) phenol) was found to have decent binding free energy (-8.4 KJ/Mol), thus this compound can be considered as a hit for development of PTP-1B inhibitors.

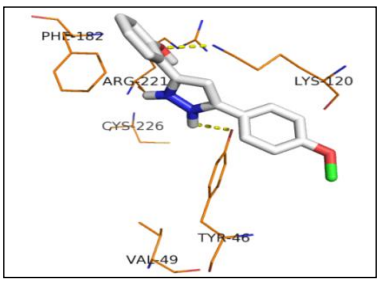


Figure 3: PTB 1B binding sites.

RESULTS AND DISCUSSION:

The synthesis of substituted chalcone derivatives 4(A-E) is outlined in Scheme 1. All the synthesized substituted chalcone derivatives 4(A-E) was characterized by 1H NMR, IR and Mass spectral data. In general the IR spectral data of all the substituted chalcone derivatives 4(A-E) indicated the presence of distinctive functional groups. The mass spectra of compounds showed (M+1) peaks, is in agreement with their molecular formula. The 1H NMR data for the chalcone derivatives 4(A-E) were also is in agreement with the assigned structures. All the compounds were evaluated for antihyperglycemic activity by observing their fall in blood glucose level towards sucrose loaded diabetic model. Pharmacological data of the compounds have been given in table. Docking scores predict that all the synthesized compounds 4(A-E) will show slight difference in activity with 4C having highest activity. These docking results are in accordance with the results of in vivo activity.

Table 3: Result of i*n vivo* Antihyperglycemic activity of synthesized derivatives

S. No.	Compounds	Percentage Antihyperglycemic Activity
1.	4-A	32.5
2.	4-B	34.0
3	4-C*	70.0
4.	4-D	49.2
5.	4-E	34.8
6.	Glibenclamide (Standard)	68.0

Data presented as % anti-hyperglycemic effect on comparison with standard group.
*indicates most potent compound.

CONCLUSION:

From the results of *in-vivo* antihyperglycemic activity, it is concluded that these molecules can be designed as a potential drugs. Among all the synthesized compound 4-C exhibited remarkable anti hyperglycemic effect which are also, supported by docking study. Therefore results of study suggested that the heterocyclic derivatives of substituted chalcone may be exploited as commercial anti hyperglycemic agents.

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