



RESEARCH ARTICLE

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Design, synthesis, characterization and *in vivo* studies of some hydroxylated chalcone derivatives as hypoglycemic agents

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ARTICLE INFO ABSTRACT



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Introduction: Low molecular weight ligands (LMWL) have a citadel reputation in the modulation of numerous therapeutic targets as a result of their smart uniqueness. The hydroxylated chalcone derivatives have been reported to be therapeutic agents owing to their capability to demonstrate multifarious pharmacological activities, however, their potential in lowering blood glucose levels is not yet explored fully.

Methods: Corresponding aldehydes and acetophenones were made to react in an alcoholic basic medium to produce the desired chalcone scaffolds. The anti-hyperglycemic potentials of the derivatives were studied using the streptozotocin-induced diabetic rat model. Compounds 3d, 3f, 3g, 3h, and 3j demonstrated excellent anti-hyperglycemic activity.

Results: Chalcone 3d, having an *ortho*-methoxy substituent in B-ring, displayed the highest hypoglycemic potential with a 26.9% lowering of blood glucose level compared to standard acarbose which exhibited a 34.7% reduction. Compounds 3a, 3c, and 3e showed the lowest activity.

Discussion: The study revealed the potential of chalcone scaffolds in lessening the blood glucose level by 7.1% to 26.9%. The *ortho*-position was observed to be high opportunistic for inducing the hypoglycemia activity as compared to *para*-position and *para*-position is, in turn, advantageous to the *meta*-position.

Conclusions: The role of various substituents in modulating this enzyme function was studied. The electron-donating groups were found to be effectual for modulation of the anti-diabetic target compared to electron-withdrawing groups.

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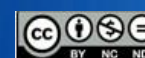
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Introduction

Insulin is an anabolic hormone which plays an imperative role in glucose metabolism (formation of glycogen, conversion of glucose into triglycerides), biomolecule synthesis (nucleic acid, protein) and translocation of essential substances (amino acids, fatty acids, and glucose) across the biological membrane (Mahapatra et al., 2019; Kuhite et al., 2017). The chronic disorder, diabetes mellitus (DM); result in elevated blood sugar levels, furthermore causing metabolic disturbance of carbohydrate, fat, and protein (Godbole et al., 2017; Borikar et al., 2017). This cumulatively affects the utilization of glucose moiety into energy by various biochemical mechanisms. The pharmacotherapeutic approach includes either delivery of insulin to recompense the malfunction of insulin creation (Type-I DM) or creating effectual management on hyperglycemic phases by activating varied biochemical components (Type-II DM) (Chhajed et al., 2017; Borikar et al., 2018). For achieving effect control, mainly five classes of therapeutic drugs are used commonly for combating hyperglycemia which acts by a different mechanism(s), however producing numerous complications. Protein tyrosine phosphatase 1B (PTP1B), aldose reductase (ALR), peroxisome proliferator-activated receptor- γ (PPAR- γ), α -glucosidase, and dipeptidyl peptidase-4 (DPP-4) remained the attractive target for researchers since eras (Borikar et al., 2018a; Gangane et al., 2018).

Low molecular weight ligands (LMWL) have citadel reputation in the modulation of numerous therapeutic targets as a result of their smart uniqueness. Natural and synthetic chalcones have demonstrated noteworthy hypoglycemic activities without major side-effects and complications (Mahapatra et al., 2017). Chalcone (1,3-diphenyl-2E-propene-1-one) is an open chemical chain transitional in aurones fabrication path of the flavones, often connoted to be the forerunners of isoflavonoids and flavonoids, have attained citadel recognition owing to LMWL features like unsophisticated chemical nature which impels straightforward developmental process with assorted alternatives for substitution and their capability to display different activities like anti-filarial, hypoglycemic, anti-platelet, hypolipidemic, anti-tubercular, anti-proliferative, antiprotozoal, antioxidant, anti-bacterial, anti-angiogenic, anti-malarial, anti-hypertensive, anti-obesity, anti-fungal, anti-arrhythmic, etc (Mahapatra et al., 2015; Mahapatra et al., 2015a; Mahapatra et al., 2015b; Mahapatra et al., 2016).

The current investigation displays the designing, synthesis, and spectroscopic characterization of ten B-ring-substituted 3/4-hydroxy chalcone derivatives and an exploration of their hypoglycemic potentials in streptozotocin-induced diabetic rats for their prospects as anti-hyperglycemic agents.

Materials and Methods

Chemicals

Streptozotocin was obtained from HiMedia Ltd., India, and Acarbose was procured as a generous gift from Zim Laboratories Ltd., Nagpur. The Glucose strips (One TouchTM) were obtained from the local pharmacy. All analytical grade chemicals employed during the experiment were purchased from Sigma-Aldrich and Merck.

Animals

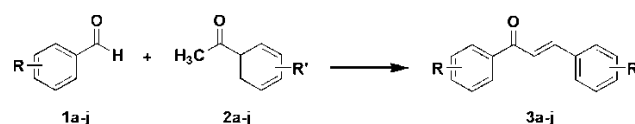
Swiss albino rats of average weight 180-250 g, aged 4-5 weeks, were employed after procuring the sanctions from the CPCSEA (1389/a/10/CPCSEA) through Department Ethical Committee. The experimental animals were kept in polypropylene cages in the approved animal house under controlled conditions (25–26°C temperature, 50–55% humidity, 12 hr light/dark cycle) with appropriate sanitized state. The experimental animals were given free access to water and were given standard pellets to feed.

Instrumentations

All weighing functions were done employing the Shimadzu[®] (Kyoto, Japan) electronic balance of model AUW220D. The infrared spectra were recorded on an infrared (IRAffinity-1) instrument using the KBr discs. The ¹H-NMR spectra and ¹³C-NMR spectra were recorded on a Bruker[®] DPX-300 Spectrospin NMR system employing Sigma-Aldrich[®] trimethylsilane (TMS) as the internal standard. The mass spectra were recorded on a JEOL-JMS-DX 303 instrument. The melting points were measured on a Perfit[®] melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on Merck[®] silica gel G-coated TLC plates.

Synthesis

The chalcones derivatives **3a-j** were synthesized according to established protocol, where corresponding aldehydes (**1a-j**) and acetophenones (**2a-j**) were made to react using ethanol as a solvent and KOH (50% v/v) (Scheme 1). The above reaction mixture was allowed to stir at room temperature for the duration of 6 hr and monitored by TLC (Mahapatra et al., 2017). The structures were identified by their melting points and spectroscopic techniques.



Scheme 1. Synthesis of chalcone derivatives (**3a-j**).

(E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (**3a**)

Yield: 78%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3410 (-OH), 3086 (s, Aromatic), 1707 (C=O), 1664 (C=C); ¹H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.81-8.0 (m, 9H, ArH), 7.59 (d, 2H, CH), 5.35 (s, 1H, OH); ¹³C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 163.9 (C-OH), 189.7 (C=O), 116.1-164.3 (Aryl C); MS (m/z): 224.1 (M^+ , 100%).

(E)-1-(3-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3b)

Yield: 53%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3404 (-OH), 3144 (s, Aromatic), 1732 (C=O), 1669 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.80-7.77 (m, 8H, ArH), 7.51 (d, 2H, CH), 5.15 (s, 1H, OH), 3.83 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.4 (C-OH), 191.8 (C=O), 114.8-164.5 (Aryl C), 55.8 (O- CH_3); MS (m/z): 254.1 (M^+ , 100%).

(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3c)

Yield: 46%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3422 (-OH), 3139 (s, Aromatic), 1723 (C=O), 1657 (C=C), 960 (C-F); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.89-8.05 (m, 8H, ArH), 7.54 (d, 2H, CH), 5.33 (s, 1H, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.6 (C-OH), 187.2 (C=O), 115.6-164.2 (Aryl C); MS (m/z): 242.1 (M^+ , 100%).

(E)-1-(4-hydroxyphenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (3d)

Yield: 65%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3413 (-OH), 3076 (s, Aromatic), 1737 (C=O), 1666 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.87-8.14 (m, 8H, ArH), 7.42 (d, 2H, CH), 5.31 (s, 1H, OH), 3.88 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 163.5 (C-OH), 189.3 (C=O), 116.7-164.5 (Aryl C), 56.2 (CH_3); MS (m/z): 254.1 (M^+ , 100%).

(E)-1-(4-hydroxyphenyl)-3-(3-methoxyphenyl)prop-2-en-1-one (3e)

Yield: 33%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3419 (-OH), 3087 (s, Aromatic), 1708 (C=O), 1678 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.85-8.12 (m, 8H, ArH), 7.38 (d, 2H, CH), 5.29 (s, 1H, OH), 3.82 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 165.1 (C-OH), 190.5 (C=O), 116.8-164.2 (Aryl C), 55.8 (CH_3); MS (m/z): 254.1 (M^+ , 100%).

(E)-3-(3,4-dimethoxyphenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3f)

Yield: 49%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3397 (-OH), 3112 (s, Aromatic), 1721 (C=O), 1652 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.9-8.2 (m, 7H, ArH), 7.58 (d, 2H, CH), 5.22 (s, 1H, OH), 3.79 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.7 (C-OH), 187.4 (C=O), 117.3-164.7 (Aryl C), 56.1 (CH_3); MS (m/z): 284.1 (M^+ , 100%).

(E)-1-(4-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (3g)

Yield: 62%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3420 (-OH), 3071 (s, Aromatic), 1699 (C=O), 1677 (C=C), 1536, 1320 ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.83-8.17 (m, 8H, ArH), 7.45 (d, 2H, CH), 5.23 (s, 1H, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.2 (C-OH), 189.2 (C=O), 115.8-165.2 (Aryl C); MS (m/z): 269.1 (M^+ , 100%).

(E)-3-(4-(dimethylamino)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3h)

Yield: 36%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3418 (-OH), 3212, 3063 (s, Aromatic), 1724 (C=O), 1654 (C=C); ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.71-7.99 (m, 8H, ArH), 7.46 (d, 2H, CH), 5.38 (s, 1H, OH), 3.06 (s, 2H, NH_2); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.9 (C-OH), 188.4 (C=O), 112.1-164.8 (Aryl C), 41.3 (CH_3); MS (m/z): 267.1 (M^+ , 100%).

(E)-3-(4-(furan-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3i)

Yield: 54%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3431 (-OH), 3108 (s, Aromatic), 1729 (C=O), 1649 (C=C), 1320 ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 6.79-8.03 (m, 11H, ArH), 7.39 (d, 2H, CH), 5.30 (s, 1H, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.4 (C-OH), 189.7 (C=O), 116.7-164.2 (Aryl C), 154 (C-O); MS (m/z): 290.1 (M^+ , 100%).

(E)-3-(4-(1H-indol-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (3j)

Yield: 71%; IR (KBr, $\nu_{\max}$ cm^{-1}): 3394 (-OH), 3180 (-NH), 3094 (s, Aromatic), 1711 (C=O), 1661 (C=C), 1320 ^1H NMR (DMSO- d_6 , 300 MHz) δ (ppm): 11.36 (s, H, NH), 6.78-8.01 (m, 13H, ArH), 7.33 (d, 2H, CH), 5.39 (s, 1H, OH); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ (ppm): 164.1 (C-OH), 188.9 (C=O), 111.4-164.9 (Aryl C), 137.3 (C-N); MS (m/z): 339.1 (M^+ , 100%).

Anti-diabetic screening of chalcones

The diabetes was induced as per the method described by Mahapatra *et al.* in the year 2018. The male albino rats having a blood glucose level in the range of 60–75 mg/dL were selected primarily. The streptozotocin was dissolved in 100 μM pH 4.5 citrate buffer and the respective solution was administered to the overnight fasted rats at 60 mg/kg b.w. i.p. dosage. After 48 hr, the level of blood glucose was evaluated using glucose strips. Those animals which displayed an elevated blood glucose level (200–300 mg/dl) were believed to be hyperglycemic. On the fourth day, the blood glucose level was checked again to confirm a steady-state hyperglycemic level. The animals exhibiting similar blood glucose levels were selected by dividing into 2 groups consisting of 6 in number. The group-I serve as the control group comprising of 1 % Gum acacia. The group-II involved screening of synthesized chalcone derivatives at 100 mg/kg b.w. dose in suspension form orally using 1% gum acacia as the carrier. Acarbose served as the reference standard. The blood glucose profile of each animal was estimated using the standard protocol. Initially, 2.5 g/kg b.w. sucrose load was administered to each animal orally, which is followed by the administration of the test sample after 30 min. The hypoglycemic potential of the novel derivatives were detected at time intervals of 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, and 300 min. The potential of chalcone derivatives in lessening the level of blood glucose was calculated as percent hypoglycemic

Compound d	R	R'	% hypoglycemic activity
3a	4-OH	4-H	8.6
3b	3-OH	4-OCH ₃	13.7
3c	4-OH	4-F	7.1
3d	4-OH	2-OCH ₃	26.9
3e	4-OH	3-OCH ₃	12.4
3f	4-OH	3 & 4- OCH ₃	20.2
3g	4-OH	4-NO ₂	21.8
3h	4-OH	4-furan (CH ₃) ₂	24.4
3i	4-OH	4-furan	19.6
3j	4-OH	4-indole	23.7
Std.	-	-	34.7

activity according to the AUC method, was to fall in AUC in group-II (experimental) average was compared to group-I (control).

Statistical analysis

The data attained from this study were represented averagely and the disparities among the treated groups and control groups were compared for the importance of employing the ANOVA which was followed by Dunnett's t-test. The *p*-values of < 0.05 were considered statistically noteworthy.

Results and discussion

Chemistry

The IR spectra revealed some prominent features of the chalcone system. The sharp peak in range 1700 cm⁻¹ - 1740 cm⁻¹ represented the ketone moiety. A wide peak at 3400 cm⁻¹ - 3430 cm⁻¹ corresponds to the hydroxyl group at 4-position. Similarly, an aliphatic alkene transition was observed for the prop-2-ene scaffold in the range of 1650 cm⁻¹ - 1680 cm⁻¹. The ¹H-NMR signified the prominent structural features. The protons present in the aromatic groups were monitored at 6.8 ppm - 8.1 ppm. The alkene protons were detected at 7.4 ppm - 7.5 ppm. The proton of the hydroxyl group was deduced at 5.25 ppm - 5.35 ppm. The ¹³C-NMR was found to agree with the ¹H-NMR. The carbon of ketone moiety was exemplified by the prominent peak at 188.1 ppm - 189.7 ppm. The values 111 ppm - 165 ppm stand for the aryl carbons in the system. The mass spectra portrayed the appearance of the base peak corresponding to their precise molecular mass. Several fragment peaks (< *m/z* 100) also appeared.

Biological activity

The study revealed that all the screened molecules exhibited immense hypoglycemic activity at a dose of 100 mg/kg b.w. in the STZ rat model. Compounds **3d**, **3f**, **3g**, **3h**, and **3j** demonstrated excellent anti-hyperglycemic activity (> 20 %), compared to standard acarbose which showed 34.7 % (Table 1).

Based on the rational designing of the pharmacophore (chalcone scaffold) and the SARs as hypoglycemic agents, the electron-donating groups like OH, NO₂, and OCH₃ play an essential role to modulate the target. Chalcone **3d**, having an *ortho*-methoxy substituent in B-ring, displayed the highest hypoglycemic potential with a 26.9 % lowering of blood glucose level. In contrast, **3f**, the analog having two electron-donating groups showed lesser activity than analogs with one methoxy group (**3d**).

Table 1. *In vivo* anti-hyperglycemic activities of hydroxylated chalcones.

Std. = Standard drug (Acarbose); Control = 1% gum acacia

The reason may be the positions of the substituents. The *ortho*-position was observed to be advantageous for the therapeutic potentials as compared to *para* position and this *para* position is in turn advantageous to *meta* (*ortho* > *para* > *meta*). Compound **3e**, having methoxy substituent at *meta*-position, somehow proves this hypothesis. The results reflected that the molecule lowered the level of blood glucose by only 12.6 %, compared to its *ortho* and *para* analogs. Compound **3a**, the unsubstituted derivative, and **3c**, the fluorinated chalcone expressed the lowest reduction in blood glucose level, with 8.6 % and 7.1 %, respectively. The reason for reduced activity may be the high lipophilic nature of **3c**, which enables higher distribution into the tissues leading to the least availability of molecules to the desired target of the action. The study also revealed the essentiality of an electron-donating group for effectual modulation of the anti-diabetic target, which electron-withdrawing group (-F) and unsubstituted analogs failed. The 4-nitro based derivatives **3g** and **3h** expressed prominent blood glucose reduction potential of 21.8 % and 24.4 %, respectively. The heterocyclic analogs **3i** and **3j** comprising of oxazole and benzopyrrole scaffold at 4-position of B-ring displayed noteworthy anti-diabetic effect of 19.6 % and 23.7 %.

Conclusions

The study divulged the budding perception of hydroxylated chalcone derivatives in reducing the blood glucose level in range 7.1 %- 26.9 %. The investigation reflected the profound role and positions of substitution on the biphenyls-prop-2-ene system. The activity was observed to augment with the substitution at *ortho* position and *para* position as compared to the *meta* position. Further, the electron-donating groups were found to be an imperative decisive factor for modulation of the anti-diabetic target.

Conflict of interest

There is no conflict of interest between the authors.

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