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Research Article

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Facile synthesis of some triazine based chalcones as potential antioxidant and anti-diabetic agents

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ABSTRACT

A series of s-triazine based chalcones have been prepared by the Claisen-Schmidt condensation. Chalcones have characteristic 1, 3-diaryl-2-propen-1-one backbone skeleton. Changes in their aryl rings have accessible a high degree of variety that have proven useful for the development of new medicinal agents with improved potency and lesser toxicity. A convenient method for the synthesis of biological active triazine based chalcones using triazine ketone and substituted benzaldehyde in dry methanol has been done. The structures of the compounds were confirmed by spectral data (IR, ^{1}H NMR and Mass spectroscopy). The synthesized compounds were studied for their antioxidant and anti-diabetic activity.

Keywords: Antioxidant, Anti-diabetic activity, Cyanuric chloride, 2-chloro-4,6-dimethoxy-1,3,5-triazine, substituted benzaldehyde, Triazine chalcone.

INTRODUCTION

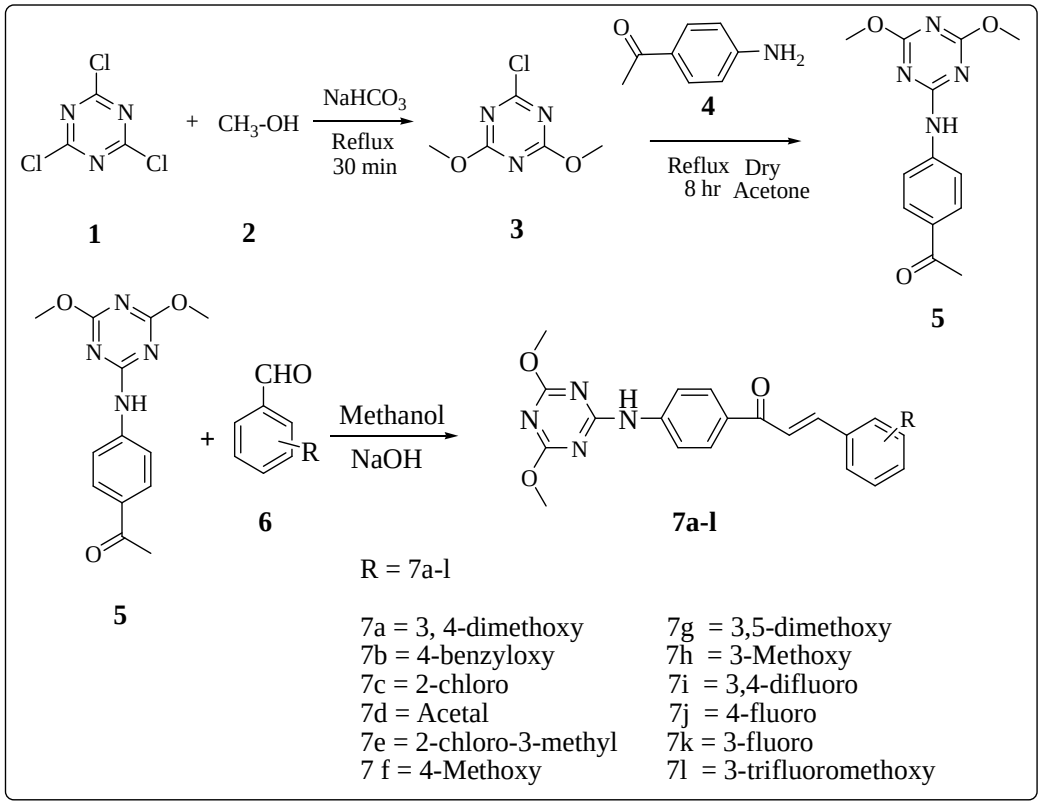
Recently, 1, 3, 5-triazine derivatives are useful extensively as biophores due to their structural similarity with naturally abundant heteroaromatic component. The 1,3,5-triazine core is also of particular interest in combinational chemistry approach due to its synthetic accessibility[1] using cyanuric chloride, three chlorine atoms can be replaced by alcohol, amine, other reagents.[2] The chalcone moiety is well know biologically active motif.[3]

The *S*-triazine core containing chalcones have their own significance in heterocyclic chemistry due to their own superior biological activity.[4,18] They found to be valuable as local anaesthetic,[5] antibacterial,[6-7] antimalerial,[8-10] antiprotozolic,[11-12] antitubercular,[13] anticancer,[14-15] antifungal activity.[16-17] The chemistry of chalcones have been recognized as a significant field of study.[19] The usefulness of manipulating the triazine scoffold and its varied biological activity have promoted us to synthesize triazine chalcones in order to study their biological activity.

The α, β unsaturated carbonyl compound is the main structure component in various naturally occurring and biological essential substances.[20] Various methods are available for the preparation of chalcones. The most convenient method is the Claisen-Schimdt condensation in which arylmethylketone react with aryl aldehyde in equimolar quantities in the presence of alcoholic alkali. It is well know that most of natural and synthetic chalcones are highly active with medicinal and pharmaceutical applications.[5-19]

In view of above benefits there is the scope for further studies on chalcones, We herein report some novel triazine based chalcones derived from triazine ketones and substituted benzaldehyde. The synthesized compounds were characterized by IR, ^{1}HNMR, Mass spectral analysis. The synthesis of intermediate and target compounds was accomplished as per steps illustrated in **scheme1**. The first step comprises the formation of 2-chloro-4, 6-dimethoxy-1, 3, 5-triazine **3** in very good yield by the nucleophilic displacement of two chlorine atoms of cyanuric chloride **1** by methoxy anion from methanol **2**. The synthesis of compound **5** was achieved by the reaction between compound **3** and 4-aminoacetophenone **4** in dry acetone at 80-90 ^{0}C for 8 hr. Sebsequient coupling of the compounds **5** with the various aromatic aldehydes **6** under basic condition (40% NaOH) in dry methanol solvent at R.T. gives rise to the corresponding triazine chalcones (**7a-l**). The reaction proceeded in good yield. The study of antioxidant activity was undertaken by diphenylpicrylhydrazyl (DPPH·) radical scavenging method and anti-diabetic activity were investigated by non-enzymatic haemoglobin glycosylation method. Finally, we wished to discover the novel bioactive compound from the most powerful antioxidant, hypoglycemic compounds.

Scheme 1: Synthesis of Some triazine based chalcones.



RESULTS AND DISCUSSION

The compound **3** was prepared by reaction of cyanuric chloride **1** (0.1 mol) with sodium bicarbonate (0.2 mol) in methanol and water to form 2-chloro-4, 6-dimethoxy-1, 3, 5-triazine (CDMT) **3**. Further, compound **3** react with 4-amino acetophenone **4** in presence of dry acetone to give the compound **5.** Subsequent condensation of triazine ketone **5** with various aromatic aldehyde **6** in presence of dry methanol led to compound **7a-l**. The structure of synthesized compounds was assigned on the basis of IR, ^{1}H NMR, mass spectral data and elemental analysis.

The IR spectrum of compound **7a-l** shows the characteristics absorption band at 1630-1640-1650 cm^{-1}due to carbonyl (C=O) group. The ^{1}HNMR of compound **7a-l** showed doublet at 6.80-6.90 ppm due to –CO-CH=CH- and doublet at 7.98-8.05 ppm due to Ar-CH=CH- which confirm the presence of chalcone moiety.

Antioxidant activity: By DPPH method, percentage inhibition was calculated and compared with the percentage inhibition of standard (Ascorbic Acid). By this method 7b, 7c, 7d, 7k, 7l showed highest antioxidant activity and compounds 7a, 7f, 7g, 7h, 7i,7j showed moderate antioxidant activity while other compounds showed 7e low antioxidant activity.

Antidiabetic activity: From this method it was showed that triazine chalcones 7e, 7i, 7j, 7k, 7l had moderate anti-diabetic activity while other compounds showed 7a, 7b, 7c, 7d, 7f, 7g, 7h low antioxidant activity.

1.3 Experimental Section

The cyanuric chloride, 4-aminoacetophenone and substituted benzaldehyde were purched from Sigma Aldrich chemicals Pvt. Ltd, Mumbai, India. All melting points were determined by open capillary method and are uncorrected. The solvent were reagent grad and which necessary were purified by either distillation or recrystallisation before use. The IR spectra were recorded with a nexus 470FT-IR spectrophotometer. The ^{1}H NMR spectra are recorded in DMSO-d_6 on a Bruker DRX-400 MHz. The chemical shift is expressed in δ unit and TMS as internal reference. The Mass spectra were obtained on Jeol-SX-102(FAB) spectrometer.

General procedure for the Synthesis of Triazine chalcone (7a-l).

It was prepared in the following three steps.

Step-I

1.3.1. Synthesis of 2-chloro-4, 6-dimethoxy-1, 3, 5-triazine (2):

Cyanuric chloride **1**(18.5 g, 0.1 mol) was dissolved in 60 ml methanol **2** and 5 ml water in a 250 ml round bottom flask and sodium bicarbonate (16.8 g, 0.2 mol) was added slowly in reaction mixture at room temperature. Then, the reaction mixture was refluxed for 30 minutes until the evolution of CO_2 was stopped. The contents were poured onto ice cold water and filtered. The white shiny solid product **3** was obtained and recrystalised from dichloromethane, dried in desiccators.

Off white shiny solid, Yield: 13 g (74%); M.P: 74-76^{0}C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 4.05 (s, 6H, of two -CH_3) ; MS (70 eV): *m*/*z* (%) = 175.67 [M^+, 78%], Anal. Calcd for $C_5H_6ClN_3O_2$: C, 34.20; H, 3.44; N, 23.93 %. Found: C, 33.98; H, 3.34; N, 23.70%.

Step-II

1.3.2. Synthesis of 1-(4-(4,6-dimethoxy-1,3,5-triazin-2-ylamino)phenyl)ethanone (5):

4-Aminoacetophenone **4** (1.35 g, 0.01 mole) and compound **3** (1.75 g, 0.01 mole) were dissolved in dry acetone (50 ml). The reaction mixture was refluxed for 8 hr. After completion of reaction, which is confirmed on thin layer chromatography ,reaction mixture were poured into ice water. The sodium carbonate solution (0.005N, 10 ml water)was added to nutralised HCl generated during condensation.The solid seprated was filtered, washed with water, dried and purified by ethylacetate and hexane to get pure product **5**.

Off Light Brown solid, Yield: 76%; M.p: 205-207 ^{0}C ; IR (KBr) 3366(NH- stretch),1660(-C=O), 804(-C-N= stret in *s*-triazine) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 3.92 (s, 6H, of two -OCH_3), 2.45 (s, 3H of -$COCH_3$) ,7.80-8.05 (m, 4H of Ar-H), 10.45 (s, 1H of Ar-NH); MS(70 ev): *m*/*z* (%) = 274.28 [M^+, 78%], Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43 %. Found: C, 56.80; H, 5.08; N, 20.17%.

Step-III

1.3.3. Synthesis of (E)-1-(4-(4,6-dimethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one. (7a):

Compound **5** (2.74g, 0.01 mole) was dissolved in methanol (40 ml) and 3,4-dimethoxy benzaldehyde **6** (1.66g, 0.01mole) was added with constant stirring at room temperature for 30 minute, then sodium hydroxide (40% w/v) was added to reaction mixture which was again stirred at R.T. for 16 hr. The progress of reaction was monitored by TLC. After completion of the reaction, crushed ice was added in the reaction mixture and nutralised with HCl. The product seprated was filtered, washed with water, dried and recrystalised from ethanol to get pure product 7**a**.

Similarly remaining compound 7**b-l** were prepared.

Characterization data for compounds (7a-l) are given as follows.

(E)-1-(4-(4,6-dimethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(3,4-dimethoxyphenyl) prop-2-en-1-one (7a):

Nature : Off pale yellow solid; M. F. $C_{22}H_{22}N_4O_5$;Yield:75% ; M.p. 110-112 °C; IR (KBr cm^{-1}) : ν = 3340 (N-H str. in 2^0 amine), 2836 (C-H str. in aromatic ring), 1629 (-C=C- str. in aromatic ring), 1234 (C-O-C Ether); 809 (C-N- str. in s-triazine) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 3.99(s, 6H, -2OCH_3 in s-triazine), 3.95 (s, 3H, m-OCH_3), 3.97 (s, 3H, p-OCH_3), 7.02(d, *J = 12 Hz* , 2H, Ar-H), 7.38-7.40(dd, *J = 12 Hz* , 2H, Ar-H), 7.54(s, 1H, Ar-H), 7.78-7.76(d, *J = 8.1 Hz*, 1H, Ar-H), 7.82(d, *J = 8.1 Hz* , 1H, Ar-H), 7.96(d, *J = 7.8 Hz* , 1H of –CO-CH=CH-), 8.23 (d, *J = 7.8 Hz* , 1H of Ar-CH=CH-), 10.45 (s, 1H, -NH) ; MS (70 eV) *m/z* : 422.16 [M^+, 100%], Anal. Calcd for $C_{22}H_{22}N_4O_5$: C, 62.55; H 5.25; N, 13.26. Found: C, 62.38; H, 5.08; N, 13.13 %.

(2E)-1-(4-(1,2-dihydro-4,6-dimethoxy-1,3,5-triazin-2-ylamino)phenyl)-3-(4-(benzyloxy) phenyl)prop-2-en-1-one (7b):

Nature : Off pale yellow solid; M. F. $C_{27}H_{24}N_4O_4$;Yield:75% ; M.p. 116-118 °C; IR (KBr cm^{-1}) : ν = 3335 (N-H str. in 2^0 amine), 2830 (C-H str. in aromatic ring), 1626 (-C=C- str. in aromatic ring), 1250 (C-O-C in ether); 804 (C-N- str. in s-triazine) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 5.18(s, 2H, -OCH_2-Ar), 3.88 (s, 6H, -2OCH_3), 7.0-7.90 (m, 13H, Ar-H), 7.96 (d, *J = 7.8* Hz,1H of –CO-CH=CH), 8.18(d, *J = 7.8* Hz, 1H of Ar-CH=CH-), 10.12 (s, 1H, NH-) ; MS (70 eV) *m/z* : 468.18 [M^+, 100%], Anal. Calcd for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96. Found: C, 69.08; H, 5.11; N, 11.83 %.

Characterization data for compounds (7c):

Nature : Off pale yellow solid; M. F. $C_{20}H_{17}N_4O_3Cl$;Yield:73% ; M.p. 118-120 °C; IR (KBr cm^{-1}) : ν = 3333 (N-H str. in 2^0 amine), 2825 (C-H str. in aromatic ring), 1600 (-CH=CH- str. in aromatic ring), 1645 (-C=O); 812 (C-N- str. in s-triazine) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 3.98 (s, 6H, -2OCH_3), 7.40-7.60 (m, 8H, Ar-H), 7.98 (d, *J = 7.8* Hz, 1H of –CO-CH=CH-), 8.20 (d, *J = 7.8* Hz, 1H of Ar-CH=CH-), 10.50 (s, 1H, -NH); MS (70 eV) *m/z* : 396.10[M^+, 100%], Anal. Calcd for $C_{20}H_{17}N_4O_3Cl$: C, 60.53; H, 4.32; N, 14.12. Found: C, 60.44; H, 4.15; N, 14.03 %.

Characterization data for compounds (7d):

Nature : Off pale yellow solid; M. F. $C_{21}H_{18}N_4O_5$;Yield:72% ; M. p. 218-220 °C; IR (KBr cm^{-1}) : ν = 3330 (N-H str. in 2^0 amine), 2846 (C-H str. in aromatic ring), 1619 (-C=C- str. in aromatic ring), 1250 (C-O-C Ether); 810 (C-N- str. in s-triazine) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 3.98 (s, 6H, -2OCH_3 in s-triazine), 6.10 (s, 2H, -O-CH_2-O-), 7.0(dd, *J = 12.36* Hz, 2H, Ar-H), 7.32(dd, *J = 12.36* Hz, 2H, Ar-H), 7.65(m, 1H, Ar-H), 7.80(s, 1H, Ar-H), 7.88(s, 1H, Ar-H), 7.95(d, *J = 7.8* Hz, 1H of –CO-CH=), 8.16 (d, *J = 7.8* Hz, 1H of Ar-CH=), 10.40(s, 1H, -NH); MS (70 eV) *m/z*:406.14[M^+, 100%],: Anal. Calcd for $C_{21}H_{18}N_4O_5$: C, 62.06; H 4.46; N, 13.79. Found: C, 61.98; H, 4.20; N, 13.53 %.

Characterization data for compounds (7e):

Nature : Off Light yellow solid; M. F. $C_{21}H_{19}N_4O_3Cl$;Yield:72% ; M.P. 110-112 °C; IR (KBr cm^{-1}) : ν = 3350 (N-H str. in 2^0 amine), 2850 (C-H str. in aromatic ring),1622(-C=O); 1633 (-C=C- str. in aromatic ring), 1239 (C-O-C Ether); 806 (C-N- str. in s-triazine), 786 (C-Cl str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 2.40 (s, 3H of –$COCH_3$) 3.98 (s, 6H, -2OCH_3 in s-triazine), 7.32-7.48 (m, 3H, Ar-H), 7.90-8.00 (m, 4H, Ar-H), 8.08 (d, *J = 7.8* Hz, 1H of –CO-CH=), 8.19 (d, *J = 7.8* Hz, 1H of Ar-CH=), 10.41 (s, 1H, -NH) ; MS (70 eV) *m/z* : 410.11 [M^+, 100%], Anal. Calcd for $C_{21}H_{19}N_4O_3Cl$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.20; H, 4.29; N, 13.43 %.

Characterization data for compounds (7f):

Nature : Off pale yellow solid; M. F. $C_{21}H_{20}N_4O_4$;Yield:75% ; M. p. 140-142 °C; IR (KBr cm^{-1}) : ν = 3330 (N-H str. in 2^0 amine), 2843 (C-H str. in aromatic ring),1640 (-C=O) 1632 (-C=C- str. in aromatic ring), 1220 (C-O-C in ether); 807 (C-N- str. in s-triazine) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: δ = 3.99(s, 6H, -2OCH_3), 3.82 (s, 3H, P-OCH_3), 7.10-7.90 (m, 8H, Ar-H), 7.98 (d, 1H of –CO-CH=), 8.18 (d, 1H of Ar-CH=), 10.47(s, 1H, -NH); MS (70 eV) *m/z* : 392.06 [M^+, 100%], Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.05; H, 5.09; N, 14.03 %.

Characterization data for compounds (7g):

Nature: Off pale yellow solid; M. F. $C_{22}H_{22}N_4O_5$; Yield:75% ; M.p. 112-114 °C; MS (70 eV) *m/z* : 422.17 [M^+, 100%], Anal. Calcd for $C_{22}H_{22}N_4O_5$: C, 62.55; H, 5.25; N, 13.26. Found: C, 62.45; H, 5.15; N, 13.13 %.

Characterization data for compounds (7h):
Nature : Off pale yellow solid; M. F. $C_{21}H_{20}N_4O_4$;Yield:74% ; M.p. 138-140 °C; MS (70 eV) *m/z* : 392.16 [M^+, 100%], Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.15; H, 5.04; N, 14.13 %.

Characterization data for compounds (7i):
Nature: Off pale yellow solid; M. F. $C_{20}H_{16}N_4O_3F_2$;Yield:74% ; M. p. 144-146 °C; MS (70 eV) *m/z* : 398.13 [M^+, 100%], Anal. Calcd for $C_{20}H_{16}N_4O_3F_2$: C, 60.30; H, 4.05; N, 14.05. Found: C, 60.15; H, 4.00; N, 13.98 %.

Characterization data for compounds (7j):
Nature : Off pale yellow solid; M. F. $C_{20}H_{17}N_4O_3F$;Yield:74% ; M.p.129-131°C; MS (70 eV) *m/z* : 380.10[M^+, 100%], Anal. Calcd for $C_{20}H_{17}N_4O_3F$: C, 63.15; H, 4.50; N, 14.73. Found: C, 63.05; H, 4.34; N, 14.50 %.

Characterization data for compounds (7k):
Nature : Off pale yellow solid; M. F. $C_{20}H_{17}N_4O_3F$; Yield:74% ; M.p.130-132°C; MS (70 eV) *m/z* : 380.13[M^+, 100%], Anal. Calcd for $C_{20}H_{17}N_4O_3F$: C, 63.15; H, 4.50; N, 14.73. Found: C, 63.05; H, 4.26; N, 14.59 %.

Characterization data for compounds (7l):
Nature: Off pale yellow solid; M. F. $C_{21}H_{17}N_4O_4F_3$;Yield:74% ; M.p.148-150°C; MS (70 eV) *m/z* : 446.14[M^+, 100%], Anal. Calcd for $C_{20}H_{17}N_4O_4F_3$: C, 56.50; H, 3.84; N, 12.77. Found: C, 56.44; H, 3.56; N, 12.65 %.

1.4 Antioxidant Activity and antidiabetic activity:
The antioxidant and anti-diabetic activity was done as per literature.[21-26]

Antioxidant Activity:
The antioxidant effect of triazine chalcones was estimated by free radical scavenging. To determine the free radical scavenging activity, a 0.1mM solution of DPPH radical in methanol was prepared and 1ml of this solution was added to 3 ml of the test material at different concentrations prepared in methanol (Huang *et al*., 2004). Solutions were incubated for 30min at room temperature and then absorbance was measured at 517 nm. The decreasing of the DPPH solution absorbance indicates an increase of the DPPH radical-scavenging activity. This activity is given as % DPPH radical-scavenging that is calculated in the equation using DPPH solution as control. The observed data for screening are presented in Tables-1.

% DPPH radical scavenging = 1-[CA-SA/CA] × 100
CA - control absorbance
SA - sample absorbance

Table-1: Antioxidant Activity of triazine chalcones.

Compounds	Antioxidant % DPPH radical	Antidiabetic % inhibition
7a	29.36	12.5
7b	49.12	19.3
7c	56.4	15.12
7d	55.21	23.85
7e	23.22	29.27
7f	27.5	10.23
7g	29.25	12.3
7h	27.4	10.20
7i	30.35	28.50
7j	32.22	30.55
7k	38.55	32.56
7l	45.30	33.22
ascorbic acid	72.25	NA
Alpha-Tocopherol	NA	46.28

NA-Not applicable

In-vitro antidiabetic activity - Non-enzymatic glycosylation of haemoglobin assay :
The antidiabetic activities[27] of Chalcones were investigated by estimating degree of non-enzymatic haemoglobin glycosylation, measured [26] colorimetrically at 520 nm. Glucose (2%), haemoglobin (0.06%) and Sodium azide

(0.02%) solutions were prepared in phosphate buffer 0.01 M, pH 7.4. The 1 ml each of above solution was mixed. The 1 ml of each chalcone solution (final concentration 10 µg/ml) of prepared sample was added to above mixture. The mixture was incubated in dark at room temperature for 72 hrs. The degree of glycosylation of haemoglobin was measured colorimetrically at 520nm. Alpha-Tocopherol (Trolax) was used as a standard drug for assay. The % inhibition was calculated as previously published protocol. All the tests were performed in triplicate. The observed data for screening are presented in Tables-1.

CONCLUSION

In this work, a series of compounds comprising of *S*-triazine based chalcone were successfully synthesized using Claisen-Schmidt condensation method. *S*-triazine based chalcone provided a versatile synthetic approach for the synthesis of differently bioactive substituted triazine chalcones. The synthetic yields of the generated products ranged from 69 to 75 % and their structures were established by spectral data (IR, NMR, and MS). Finally, all of synthesized compounds have been tested for their antioxidant and anti-diabetic activities. The antioxidant activity by DPPH method was calculated and compared with the percentage inhibition of standard (Ascorbic Acid). The synthesized compounds 7c, 7i, 7k, 7l showed highest while compounds 7b, 7d, 7j exhibit moderate and the compounds 7a, 7e,7f, 7g, 7h showed low antioxidant activity. The anti-diabetic active compounds (7e, 7i, 7j, 7k,7l) shared a common feature with substitution at position 2,3,4 of benzaldehyde ring, suggesting the significance of substitution at this position for glucose uptake activity. Additionally, compounds (7k and 7l) with fluoro substitution at position 3 on benzaldehyde ring also showed great potential in reducing glucose medium concentration.

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