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Design and Synthesis of novel Chalcone Derivatives and their Antioxidant Activity

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Abstract: *A simple and effective synthesis of pyrazoles and cyanopyridines derivatives from Chalcone according to Claisen-Schmidt condensation. Chalcone, (2E)-N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)-3-(p-tolyl) acrylamide* ***(5)*** *have been prepared. Further this chalcone with hydrazine hydrate gives pyrazoles* ***(6)*** *and on reaction with malononitrile gives cyanopyridines* ***(7)****. The structure of the newly synthesized compounds have also been screened for their antioxidant activities and it was characterized by IR, [1] H NMR and [13]C NMR spectral data.*

Keywords: *Chalcones, Claisen-Schmidt condensation, pyrazoles, cyanopyridines, antioxidant activity.*

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I. Introduction

Chalcones have close relation to flavanoid family. Recently, several articles dealing with chalcone compounds have important application in medicinal field. Chemically these are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are bound by an α,β-unsaturated carbonyl group. Chalcones undergo a different type of chemical reactions that leads to some heterocyclic compounds [1-3].

The simplest method involves Claisen-Schimdt condensation of equimolar of aromatic aldehyde with substituted acetophenone gives chalcones in base medium, which producing pyrazole and pyrazoline derivatives respectively. We report here the synthesis of some novel pyrazole derivatives and tested for their antibacterial and antioxidant activities and are popular intermediates for synthesizing various type of heterocyclic compounds having therapeutic value [4,5]. Some of the important type of reaction, chalcones undergo ring closure reaction with hydrazine, guanidine, malononitrile etc. gives heterocyclic derivatives such as pyrazoline , pyrimidine, iso-oxazole and cyanopyridine [6].

The compounds with the backbone of chalcones have shown interesting biological activities including antimalarial[7], antibacterial[8], antituberculosis[9], anticancer[10], anti-inflammatory[11], antifunga[12], antioxidant[13], antileishmanial[14].

II. Experimental

Materials and Methods

All chemicals and reagents were commercially available and used in the present project were of AR and LR grade, procured from Aldrich, Hi-media and Sigma and used without further purification. Melting points were determined by open glass capillary method on a melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography on silica gel plates. The eluent was a mixture of n-hexane/ethyl acetate in 8:2 ratio and the spots were identified by UV. IR spectra were recorded with KBr on Perkin Elmer 1600 FT-IR (4000-400cm^{-1}) spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined by using Bruker 400 MHz with $CDCl_3$ as solvent & TMS as internal reference.

Synthesis of N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)acetamide(3)

Equimolar quantities of 2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-one (0.01mol) and 4-aminoacetanilide (0.01mol) were dissolved in 40mL ethanol. The reaction mixture was refluxed using water bath for 6hrs. The sodium hydroxide is dissolved (0.01mol, 1g) in 10mL of water was added drop wise to neutralized HCl evolved during the reaction. Finally, the reaction mixture was cooled and poured into crused ice. The solid separated out was filtered, washed with water and recrystallized from ethanol to give compound (3). Brown powder, TLC (Hexane: Ethylacetate, 8:2).

Synthesis of (2E)-N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)-3-(p-tolyl)acryl amide(5)

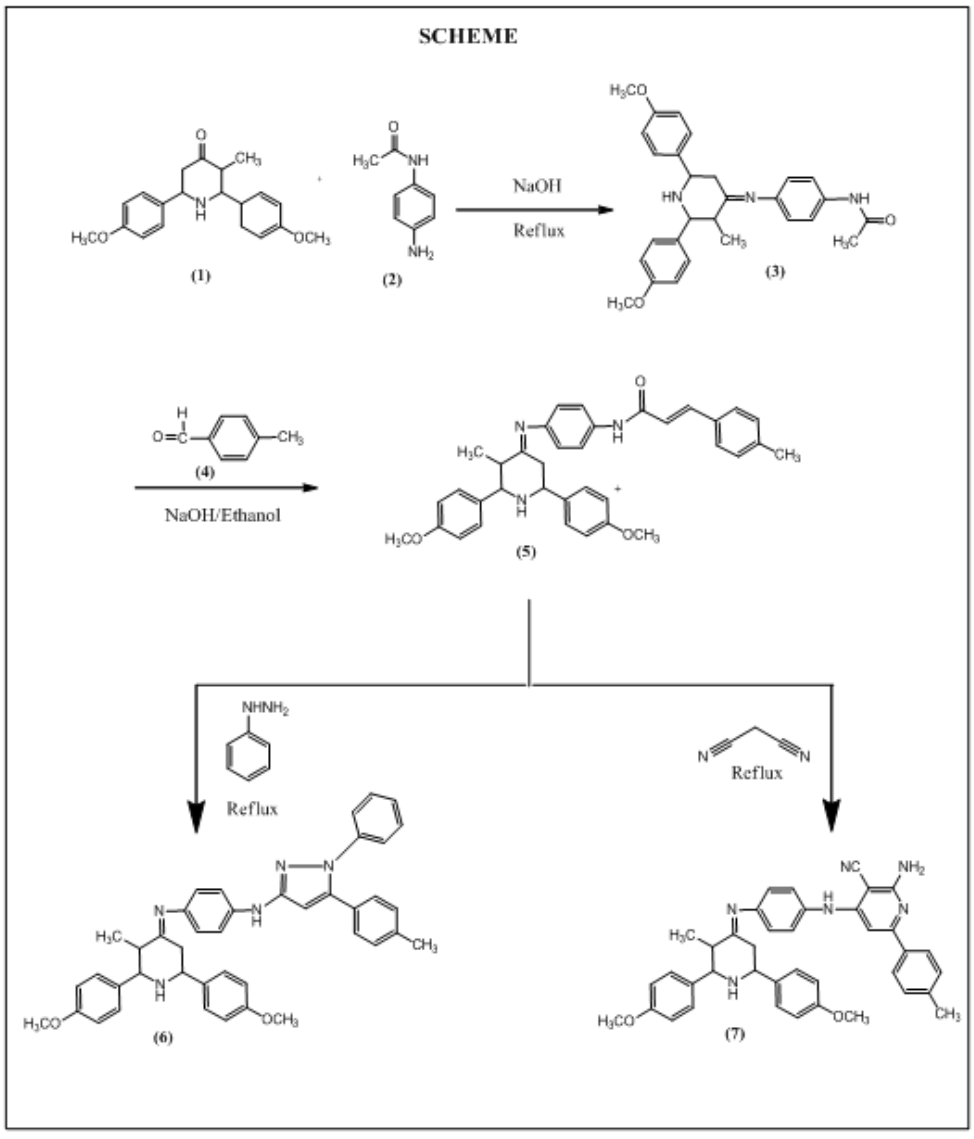
A mixture of N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)acetamide (0.01mol) and p-tolualdehyde (0.01mol) was stirred ethanol (30mL) and then an aqueous Solution of NaOH (10%), 25mL) was added slowly and the mixture continuously stirred for 4-hours. Then it was poured into 400mL of cold water (distilled water) with constant stirring and left overnight in refrigerator. The precipitate is obtained was filtered and recrystallized from ethanol. Yellow powder, TLC (Hexane: Ethylacetate, 8:2).

Synthesis of (E)-N^1-(2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)-N^4-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)benzene-1,4-diamine(6)

A mixture of (2E)-N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)-3-(p-tolyl)acrylamide (0.01mol) and Phenyl hydrazine (0.01mol) were dissolved in 30mL ethanol. The reaction mixture was refluxed using water bath for 6hrs. The pottasium hydroxide is dissolved (0.01mol, 1g) in 10mL of water was added drop wise to neutralized HCl evolved during the reaction. Finally, the reaction mixture was cooled and poured into crused ice. The solid separated out was filtered, washed with water and recrystallized from ethanol. Turbid white powder, TLC (Hexane: Ethylacetate, 8:2)

Synthesis of 2-amino-4-((4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl) amino)-6-(p-tolyl) nicotinonitrile(7)

A mixture of (2E)-N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)-3-(p-tolyl)acrylamide (0.0007mol), malononitrile (0.0014mol) and ammonium acetate(0.0007mol) were dissolved in 30mL ethanol. The reaction mixture was refluxed using water bath for 8hrs. Finally, the reaction mixture was cooled and poured into crused ice. The solid separated out was filtered, washed with water and recrystallized from ethanol. Dark brown powder, TLC (Hexane: Ethylacetate, 8:2).



SCHEME 1. Synthesis of novel chalcone derivatives

III. Results And Discussion

FT-IR, ^{1}H NMR and ^{13}C NMR

N-(4-((2,6-bis(4-methoxyphenyl)-3-methyl piperidin-4-ylidene)amino)phenyl)acetamide(3)

IR:(KBr, cm $^{-1}$) 3398 (N-H), 2921 (Aromatic C-H stretch, 1712 (NH-C=O), 1599 (C=N stretch).

(2E)-N-(4-((2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)amino)phenyl)-3-(p-tolyl)acryl amide(5)

IR:(KBr, cm $^{-1}$) 3367(N-H), 2922 (Aromatic C-H stretch, 1683 (NH-C=O), 1571 (CH=CH of carbonyl conjugated double band), 1545 (C=N stretch).

(E)-N^{1}-(2,6-bis(4-methoxyphenyl)-3-methylpiperidin-4-ylidene)-N^{4}-(1-phenyl-5-(p-tolyl)-1H-pyrazol-3-yl)benzene-1,4-diamine(6)

IR:(KBr, cm $^{-1}$) 3373(N-H), 3007 (Aromatic C-H stretch), 2928 (C-H stretch), 1601 (C=N stretch), 1260 (C-N stretch). ^{1}H NMR ($CDCl_3$) δ ppm: 6.1 to 7 (pyrazole C-H), 7.1 to 8.0 (m, Ar C-H), 3.6 to 4.1 (d, Ar N-H). ^{13}C NMR ($CDCl_3$)δ ppm: 53 (Aliphatic-CH_2), 127 (pyrazole-C), 118(Ar-C).

2-amino-4-((4-((2,6–bis(4-methoxyphenyl)–3–methylpiperidin–4-ylidene)amino)phenyl)amino)-6-(p-tolyl) nicotinonitrile(7)

IR:(KBr, cm $^{-1}$) 3396 (N-H), 2921 (Aromatic C-H stretch), 2841 (C-H stretch), 1615 (C=N stretch), 1253 (C-N stretch).). ^{1}H NMR ($CDCl_3$) δ ppm: 6.7 to 7.5 (Ar-H), 0.9 (CH_3), 2.7(OCH_3), 4.2 (Ar-NH_2). ^{13}C NMR ($CDCl_3$)δ ppm: 24 (Aliphatic-CH_3), 115 (Ar-C), 55(OCH_3), 153(Cyanide).

Table 1: Physical Data of synthesized compounds

Compound	Mol.formula	Mol.weight	m.p (^{0} C)	R_f Value	Yield (%)
(3)	$C_{28}H_{31}N_3O_3$	457.56	128-130	0.56	75
(5)	$C_{36}H_{37}N_3O_3$	559.70	110-115	0.77	80
(6)	$C_{42}H_{43}N_5O_2$	649.82	188-190	0.68	74
(7)	$C_{39}H_{38}N_6O_2$	622.76	102-104	0.64	79

IV. *In Vitro* Antioxidant Activity

DPPH scavenging activity of synthesized compounds displayed to table.2 The results of the antioxidant activity of the newly synthesized compounds were found to be excellent activity comparable antioxidant potential with the standard ascorbic acid. Remaining compound have showed a moderate activity.

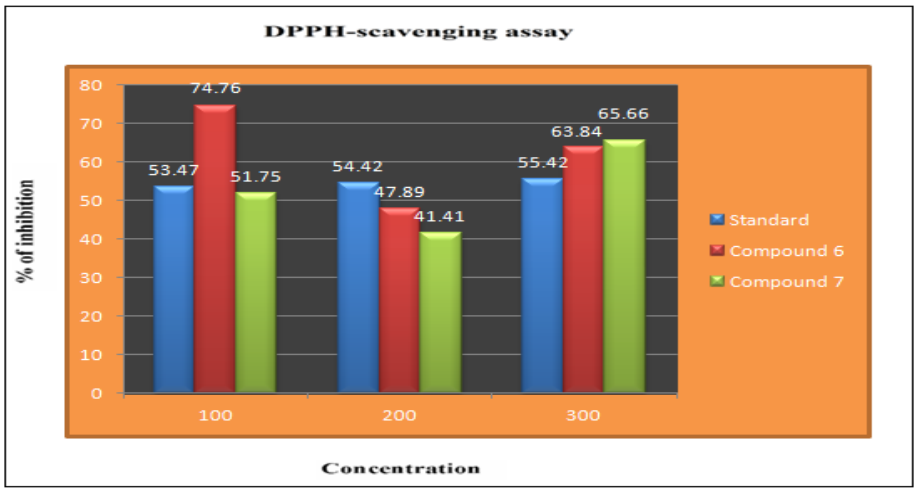


Table : 2 Antioxidant results with %Inhibition

Concentration (ppm)	Standard	%Inhibition	Comp.6	%Inhibition	Comp.7	%Inhibition
100	0.542	53.47	0.562	74.76	0.294	51.75
200	0.544	54.42	0.705	47.89	0.627	41.41
300	0.540	55.42	0.416	63.84	0.438	65.66

V. Conclusion

In the present study a synthesis of new chalcone carried out by the reaction of 4-aminoacetanilide and p-tolualdehyde with 10% NaOH in ethanol by stirring. The structure of the product has been characterized by FT- IR, ^{1}H NMR, ^{13}C NMR spectroscopy data and the purity of this compound was analyzed by T.L.C. Technique. In overview, we have synthesized new series of chalcone derivatives containing a phenyl hydrazine and malononitrile moiety and evaluated their antioxidant activity. Compound **6** showed excellent antioxidant activity.

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