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''DESIGN, SYNTHESIS AND CHARACTERIZATION OF SOME NEW 2-AMINO PYRIMIDINE DERIVATIVES''

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ABSTRACT

2-substituted derivatives of indane-1,3-diones have shown many activities. Chalcones possess a number of biological and pharmacological activities such as antibacterial, antifungal, antimalarial, anti-inflammatory, anticancer, anti-tubercular, and antioxidant activities etc. The synthesis of chalcone compounds incorporating with heterocycles became great importance in medicinal chemistry. Literature survey revealed that Chalcones and Pyrimidine derivatives possess a broad spectrum of biological activities like antimicrobial, anti-inflammatory, antimalarial, antitubercular, anticancer, antidepressant and antamoebic etc.Hence an attempt is made to synthesize some new chalcones from 2- acetyl-indane- 1,3- dione with various substituted aromatic/ heteroaromatic aldehydes by the Claisen – Schmidt condensation. The resulted chalcones have been converted into their 2-amino pyrimidine derivatives by reaction with guanidine hydrochloride. The resulted compounds were identified by physical and spectral methods and were also screened for their antibacterial and antifungal activities based on the reported literature.

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INTRODUCTION

In the development of organic therapeutic agents, pharmaceutical scientists have explored numerous approaches in finding and developing organic compounds that are now available to us in dosage forms suitable for the treatment of our ills and often for the maintenance of our health. The present work deals with evaluation of antimicrobial activity of various aldehyde derivatives synthesized by Knoevenagel condensation method and substitution in the second position of indane-1, 3-dione nucleus[1-5]. The last two decades have witnessed profound changes in indane-1,3-dione chemistry in both quality and quantity.

The compounds with chalcone as backbone have been reported to possess varied biological and pharmacological activities including antimicrobial[6-9], anti-inflammatory, analgesic, antitumor, antimalarial, antitubercular[10-12], antiviral, antiulcerative, antioxidant, antihistaminic, antihyperglycemic, antihyperlipidemic and antiplatelet activities.

Pyrimidine derivatives in medicinal chemistry have been well known for their therapeutic application[13-17]. One possible reason for their activity is the presence of a pyrimidine base in thymine, cytosine and uracil, which are essential building blocks of nucleic acids, DNA and RNA. Considering this assumption 2-amino yrimidine has attracted substantial interest of synthetic biochemists.

MATERIALS AND METHODS:

Chemicals :

The organic solvents such as ethanol, acetone, chloroform and ethyl acetate and N,N-dimethyl formamide were of spectral grade and used as such without further purification. Some of the solvents were purchased from the local manufacturers and S.D Fine Chemicals Ltd, Mumbai, India. The aldehydes used in the synthesis of new chalcones viz. 4-fluorobenzaldehyde, 2,6-dinitro benzaldehyde, 3-nitro-4-chloro benzaldehyde, 5-fluoro,3-methoxy benzaldehyde, 2,6-dimethoxy benzaldehyde, 2,6-dimethoxy,4-hydroxy benzaldehyde, were purchased from SD fine Chemical Ltd. Mumbai. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The separation of the compounds was checked on TLC under UV lamp and also by spraying the plates with 10% sulphuric acid or phosphomolybdic acid or ninhydrin solution.

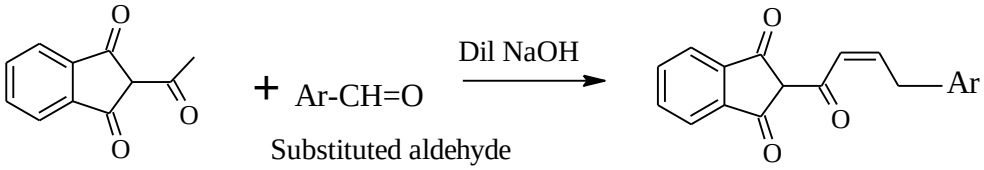
Instrumentation :

All the melting points were determined in open capillaries, using Elico digital melting point apparatus, expressed in ^{o}C and are uncorrected. Infrared spectra (IR) were recorded on BRUKER ALPHA FT-IR Spectrophotometer with Sodium chloride optics. Samples were screened in Potassium bromide (KBr) pellets and the values are expresses in cm^{-1}. The ^{1}H NMR spectra of the compounds were recorded on BRUKER Avance 400 MHz Nucliur Magnetic Resonance Spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. Mass spectra are recorded on LCMS-2010A DATA REPORT SHIMADZU (Positive/Negative ion electro sprey ionization method) Mass spectrophotometer with a 70 eV (ESI probe), using positive mode ionization method.

Experimental :

General procedure for the synthesis of chalcones of indane-1,3-dione (1a-e) :

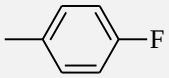
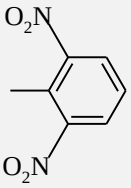
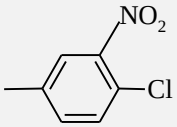
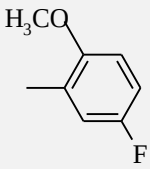
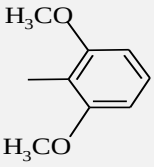
A mixture of 2-acetylindane-1,3-dione (0.01 mol) and substituted aromatic aldehyde (0.01 mol) were stirred in ethanol (25 ml) for 1 h and then an aqueous solution of sodium hydroxide (10 ml) was added to it. The mixture was then kept overnight at room temperature and then poured into crushed ice. The solution was acidified with dilute hydrochloric acid. The chalcone derivatives of indane-1,3-dione precipitates out. Then the product was filtered and recrystallized form ethanol[18],(Scheme 1).



2-Acetyl indane-1,3-dione

Substituted Chalcones of indane-1,3-dione (1a-f)

Scheme1: Synthesis of Chalcones of indane-1,3-dione.

Compound Code	1a	1b	1c	1d	1e
Ar					

2-[3(4-flourophenyl) prop-2-enoyl] indane-1,3-dione, 1a:

IR (KBr) cm^{-1} : 3142.22(Ar C-H), 2920.49(Al C-H),1684.84 (C=O), 1636.53 (CH=CH), 1541.56(Ar C=C), 1436.41(C-H), 34.33(C-F). ^{1}H NMR (δ,ppm: 7.26-7.86(m,8H Ar), 6.91(d,J=16Hz,1H), 6.34(d,J=16Hz,1H), 3.13(s,1H). Mass(m/z):296 (M^+ +2)

2-[3(2,6-dinitrophenyl) prop-2-enoyl] indane-1,3- dione, 1b:

IR (KBr) cm^{-1} : 3144.16(Ar C-H), 2922.07(Al C-H), 1692.47 (C=O), 1611.87(CH=CH), 1513.13(Ar C=C), 1467.09(C-H), 1379.19(N-O). ^{1}H NMR (δ,ppm: 7.26-7.81(m,7H Ar), 7.14(d,J=15.8Hz,1H), 6.56(d,J=15.8Hz,1H), 3.31(s,1H). Mass(m/z): 366 (M^+ Peak)

2-[3(4Chloro-3-dinitro phenyl) prop-2-enoyl] indane-1,3-dione, 1c:

IR (KBr) cm^{-1} : 3181.63(Ar C-H), 2924.81(Al C-H), 1704.59(C=O), 1635.22(CH=CH), 1523.45(Ar C=C), 1445.38(C-H), 1382.67(N-O), 737.99(C-Cl). ^{1}H NMR (δ,ppm: 7.17-8.14(m,7H Ar), 6.86(d,J=15.9Hz,1H),6.43(d,J=15.9Hz,1H), 2.93(s,1H). Mass(m/z):356 (M+peak).

2-[3(5-Flouro-2-methoxy phenyl) prop-2-enoyl] indane-1,3-dione, 1d:

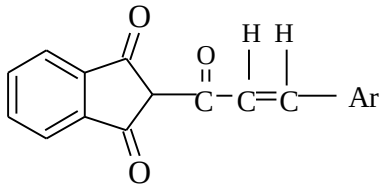
IR (KBr) cm^{-1} : 3169.53(Ar C-H), 2902.54 (Al C-H), 1688.37 (C=O), 1652.63 (CH=CH), 1536.72(Ar C=C), 1467.39 (C-H), 1228.76 (O-CH_3), 739.64 (C-F). ^{1}H NMR (δ,ppm: 7.42-8.10(m,8H Ar), 6.89(d,J=15.8 Hz,1H), 6.34(d,J=15.8 Hz,1H),2.82(s,3H);

2-[3(2,6-dimethoxy phenyl) prop-2-enoyl] indane-1,3-dione, 1e:

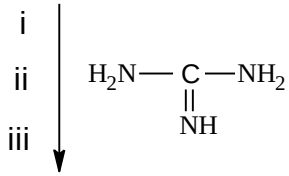
IR (KBr) cm^{-1}:3142.43(Ar C-H), 2929.67(Al C-H), 1693.41(C=O), 1649.17(CH=CH), 1594.69 (Ar C=C), 1473.42(C-H), 1261.60(O-CH3). ^{1}H NMR (δ,ppm: 7.39-8.12(m,7H Ar), 6.74- 6.80(d,J=15.4 , 6.20 (d,J=15.4 Hz, 1H), 2.69(s,1H), 3.82(s,6H,O-CH_3).

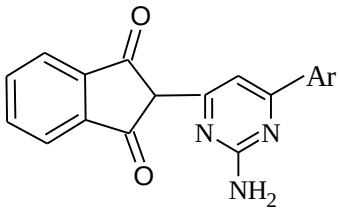
General procedure for the synthesis of new 2-amino pyrimidines:

The condensation of the chalcones with guanidine hydrochloride in an alkaline medium viz., in sodium hydroxide in the presence of ethanol as a solvent, at reflux temperatures (4 to 6 hours) resulted in the formation of corresponding 2-amino pyrimidines[19,20] (Scheme 2). Completion of the reaction was established by TLC using silica gel-G. After completion of the reaction, the reaction mixture was poured onto crushed ice with constant stirring. The solid that separated was filtered, dried and purified by recrystalliation in ethanol. The purified pyrimidine derivatives were obtained as light to bright yellow coloured powders.



Chalcones of indane-1,3-dione (1a-e)





i) NaOH, ii) Ethanol, iii) Reflux for 3 to 6 hrs.

Scheme 2 : Synthesis of new 2-Amino pyrimidines of indane-1,3-dione

2-[6-(4-Flouro phenyl)-2-Amino-1,2,5,6-tetra hydroPyrimidin-4yl]-indane-1,3-dione, 2a:

IR (KBr) cm^{-1}: 3416.33(NH_2),3036.20(Ar C-H st), 2888.14(Al C-H),1702.27 (C=O st), 1621.70 (C=N st), 1594.56(Ar C=C st), 1242.12(C-N st), 853.45(C-F st). ^{1}H NMR (δ,ppm: 6.86(s,2H, NH_2), 7.62(2H,d,J=7.4 Hz, -C-3" & 5"-H),7.73(1H,s, C-5'-H), 8.02(2H,d,J=4Hz, C-2" & 6"- H), 3.10(s,1H,C-2-H). Mass(m/z):335 (M^+ +2)

2-[6-(2,6-Dinitro phenyl) -2-Amino-1,2,5,6-tetra hydroPyrimidin -4yl]-indane-1,3-dione,2b:

IR (KBr) cm^{-1}:3407.20(NH_2), 3042.47(Ar C-H st),2892.29(Al C-H),1708.61 (C=O st), 16227.58 (C=N st), 1569.09(Ar C=C st), 1232.12(C-N st). ^{1}H NMR (δ,ppm: 6.92(s,2H, NH_2), 6.5-7.3(m,7H,Ar),7.75(1H,s, C-5'-H),3.34(s,1H,C-2-H). Mass(m/z): 408(M+peak).

2-[6-(4-Chloro,3-nitro phenyl) -2-Amino-1,2,5,6-tetra hydroPyrimidin -4yl]-indane-1,3-dione, 2c:

IR (KBr) cm^{-1}:3427.38(NH_2),3027.57(Ar C-H st), 2890.22(Al C-H st),1697.28 (C=O st),1632.05 (C=N st), 1572.19(Ar C=C st), 1238.12(C-N st), 843.45(C-Cl). ^{1}H NMR (δ,ppm: 6.89(s,2H, NH_2), 7.31-7.69(m,7H,Ar), 7.81(1H,s, C-5'-H),3.37(s,1H,C-2-H). Mass(m/z):396(M+peak).

2-[6-(3-Flouro,6-methoxy phenyl) -2-Amino-1,2,5,6-tetra hydroPyrimidin -4yl]-indane-1,3-dione, 2d:

IR (KBr) cm^{-1}:3407.41(NH_2),3045.25(Ar C-H t), 2896.33(Al C-H),1689.12 (C=O st), 1608.40 (C=N st), 1568.35 (Ar, C=C t), 124.08(C-N st), 1163.22(OCH_3). ^{1}H NMR (δ,ppm: 6.95(s,2H, NH_2),7.60-7.83(m,7H,Ar), 7.53(1H,s, C-5'-H), 3.33(s,1H,C-2-H).

2-[6-(2,6-Dimethoxy phenyl) -2-Amino-1,2,5,6-tetra hydroPyrimidin -4yl]-indane-1,3-dione,2e:

IR (KBr) cm^{-1}:3424.53(NH_2),3029.32(Ar C-H st), 2912.40(Al C-H st),1693.27 (C=O st), 1628.29 (C=N st), 1575.09 (Ar,C =C st), 1235.17(C-N st), 1178.29(OCH_3). ^{1}H NMR (δ,ppm: 6.79(s,2H, NH_2), 7.59-7.64(m,7H,Ar), 7.76 (1H,s, C-5'-H), 3.69 (s,1H,C-2-H).

RESULT & DISCUSSION

2-acetylindane-1,3-dione was treated with different aldehydes in presence of dilute base to form various chalcones of indane-1,3-dione by base catalyzed Claisen Schmidt condensation reaction. Structures of these compounds were supported by spectral data. IR spectra of carbonyl group of chalcone showed absorption bands at 1684-1699 cm^{-1}. Absoption bands at 1631-1649 corresponds to CH=CH of chalcones. Absorption band observed in the range of 7.1-8.2 ppm may be attributed by aromatic stretching vibration while that seen at 6.9-7.2 and 6.3-6.8 ppm (J =15.6-16) corresponds to CH=CH stretching.

Table 1: Physicochemical parameters of chalcones of indane-1,3-dione (1a-e):

Compound Code	Molecular Formula	Relative Molecular Mass	Melting Point (˚C)	Appearance	Percentage Yield (%)	Rf value*
1a	$C_{18}H_{11}O_3F$	294	165-166	Yellow Crystals	61	0.75
1b	$C_{18}H_9N_2O_7$	365	156-157	Yellow Crystals	63	0.72
1c	$C_{18}H_{10}NO_5Cl$	355	162-164	Brownish yellow crystals	58	0.73
1d	$C_{18}H_{13}O_4F$	312	168-169	Brownish yellow crystals	59	0.77
1e	$C_{20}H_{16}O_5$	336	167-168	Yellow Crystals	60	0.84

*M obile Phase: Ethyl acetate: Pet. ether (3:1)
Recrystallization solvent: Ethanol.

Table 2 : Physicochemical parameters of 2-Amino pyrimidines of chalcones.(2a-e):

Compound Code	Molecular Formula	Relative Molecular Mass	Melting Point (˚C)	Appearance	Percentage Yield (%)	Rf value*
2a	$C_{19}H_{12}N_3O_2F$	333	153-154	Yellow Crystals	52	0.69
2b	$C_{19}H_{11}N_5O_6$	405	156-157	Brownish yellow crystals	54	0.68
2c	$C_{19}H_{11}N_4O_4Cl$	394.5	162-163	Yellow Crystals	56	0.70
2d	$C_{20}H_{14}N_3O_3F$	363	160-161	Brownish yellow crystals	51	0.67
2e	$C_{21}H_{17}N_3O_4$	375	162-163	Yellow Crystals	55	0.70

* Mobile Phase: Ethyl acetate: Pet. ether (3:1)
Recrystallization solvent: Ethanol.

CONCLUSSION

A number of heterocyclic systems can be successfully synthesized from diaryl-propene-2-ones, popularly called as chalcones, which in turn may be obtained by Claisen-Schmidt condensation reaction. The resulting chalcones, after purification and characterization by physical and spectral methods have been converted successfully into their 2-amino pyrimidine derivatives by reaction with guandine hydrochloride which then were identified by IR, ^{1}HNMR and Mass spectral data and chemical mehods based on the reported literature.

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CONFLICT OF INTEREST

No conflict of interest.

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