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Synthesis and Biological Evaluation of Some New Chalcone and Pyrimidine Derivatives

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Abstract:
Some new chalcones and pyrimidine derivatives were prepared from 1-cyclopropyl-2-(2'-fluorophenyl)ethanone. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Keywords: *1-cyclopropyl-2-(2'-fluorophenyl)ethanone, Chalcone, Pyrimidine, antimicrobial activities*

1. Introduction

Chalcones [1] are well known and important intermediates for the construction of various heterocyclic derivatives because of the presence of reactive keto-ethylenic group. The literature review revealed that chalcone derivatives possess interesting biological activities such as Anti-inflammatory [2], antimicrobial [3], Antimalarial [4], anti-viral [5], anti-tuberculosis [6], anti-tumour [7], Antimalarial [8] activity due to the presence of reactive α, β –unsaturated keto function in chalcones. Chalcones constitute an important group of natural products and some of them possess a wide range of biological activity such as antibacterial, antitubercular [9], anticancer [10], antitumour [11] etc. Chalcone is also useful intermediate in biosynthesis of flavonides, which are substances widespread in plant.

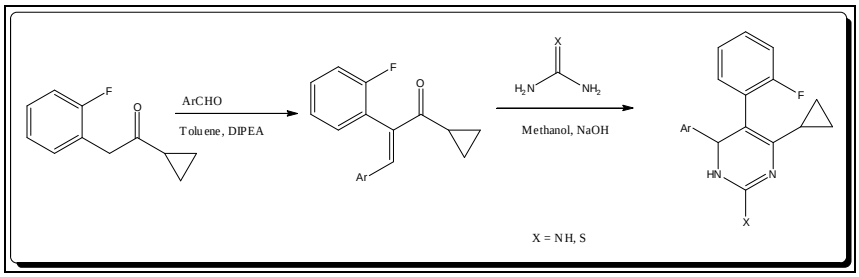
Pyrimidine is the most important member of all the diazines as this ring occurs widely in living organisms. The chemistry of Pyrimidine has been widely studied. Pyrimidine derivatives occur widely in nature showing remarkable pharmaceutical importance because of their diverse pharmacological activities. The literature review Showed that pyrimidine derivatives possess interesting biological activities such as Anti-malarial [12], Antitubercular [13], Antidiabetic [14], Anticonvulsant [15], Analgesic [16], Tranquilizer [17], Antibacterial [18], Antihypertensive [19] and Anti-cancer [20].

Chalcones and Pyrimidines have attracted attention of medicinal chemistry for both with regard to heterocyclic chemistry and the pharmacological activities associated with them, inspired us to synthesize 1-cyclopropyl-2-(2'-fluorophenyl)-3-aryl prop-2-en-1-one (1a–1l), 2-Amino-4-aryl-6-cyclopropyl-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (2a–2l) and 4-Aryl-6-cyclopropyl-2-mercapto-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (3a – 3l).

The structure of synthesized compounds was assigned based on Elemental analysis, I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method [21] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against varieties of bacterial strains such Staphylococcus aureus, Escherichia coli, Bacillus megaterium, Salmonella taphimurium and fungi Aspergillus niger at 50 µg concentration. Standard drugs like Amoxycillin, Chloramphenicol, ciprofloxacin and Griseofulvin were used for comparison purpose (Table-2).

2. Results and Discussion

The synthesis of 1-cyclopropyl-2-(2'-fluorophenyl)-3-aryl prop-2-en-1-one (1a–l), 2-Amino-4-aryl-6-cyclopropyl-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (2a–2l) and 4-Aryl-6-cyclopropyl-2-mercapto-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (3a–3l) was carried out in two steps, first by the condensation of 1-cyclopropyl-2-(2'-fluorophenyl)ethanone with different aromatic aldehyde by Claisen-shmidt condensation in presence of base catalyst to give chalcone derivatives (1a - l), which in next step were refluxed with guanidine hydrochloride and thiourea to yield pyrimidine derivatives (2a-l and 3a -l) respectivly. (Scheme-1)



Scheme-1

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR, ^{1}H-NMR, and mass spectral data.

2.1. Antibacterial Activity

It has been observed from the microbiological data that all compounds (1a-l), (2a-l) and (3a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. However the maximum activity was observed in compounds (1b),(1k),(2e),(2h),(2l),(3c), (3f), (3i) against S.aureus. The significant activity was observed in compounds (1e),(1i), (1k),(2c),(2j),(3g), (3j), (3l) against B. megaterium. The maximum activity was displayed by the compounds (1c), (1g), (1j), (1l), (2c), (2j), (3a), (3d), (3h), (3l) against E.coli. The compounds (1f),(1i), (1l),(2d),(2h),(2k), (3e), (3i) and (3l) were comparatively more effective against S taphimurium.

2.2. Antifungal Activity

The antifungal data revealed that compounds were mild to moderately toxic to the fungal strain. However comparable activity was shown by the compounds (1b),(1g),(1j),(2d),(2g),(2i),(3b),(3h), (3k) against A niger. The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Penicillin and antifungal activity was compared with standard drug viz. Griseofulvin.

2.3. Experimental Section

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-8400-IR Spectrophotometer and , 1H-NMR spectra on Bruker spectrometer (300MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of 1-cyclopropyl-2-(2'-fluorophenyl)-3-aryl prop-2-en-1-one (1a-l):

A mixture of 1-cyclopropyl-2-(2'-fluorophenyl)ethanone (0.05618Moles), DIPEA (0.00561moles), and aromatic aldehyde (0.0618moles) in Toluene(5.0 vol) was reflux and azeotropically separates out water by Dean-Stark apparatus during 3-4hrs. The progress of reaction was monitored by TLC. After completion of reaction cool the reaction mixture and charged 5% aqueous $NaHSO_3$solution and aqueous and organic phase were separated. Concentrated organic phase under reduced pressure and residue was purified by column chromatography over silica gel using hexane: ethyl acetate (9:1) to yield compound (1a-l).

(E)-1-cyclopropyl-2-(2'-fluorophenyl-3-(4-methoxyphenyl)prop-2-en-1-one (1g):

Yield = 78%, Yellow oil, IR: ν 3009 arometic C-H Str.), 2956, 2935,2838 (Alkane C-H str.), 1674(C=O Str.), 1511 (Aromatic C=C str.), H^1 NMR ($CDCl_3$): δ 0.82-0.88 (m, 2H, Cyclopropyl ring), 1.12-1.16 (m, 2H, Cyclopropyl ring), 3.73 (s,3H, -OCH_3), 6.69-7.39 (m, 8H, ArH), 7.78 (s,1H, -C=CH-), Mass m/z = 297.2, MF $C_{19}H_{17}FO_2$

General procedure for the preparation of 2-Amino-4-aryl-6-cyclopropyl-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (2a – 2l)

A mixture of Chalcones (1a-l) (0.01M) , Thiourea(0.011M) and NaOH (0.011M) in methanol was refluxed with stirring about (6-8 hrs) until complete the reaction. Reaction progress was monitor by TLC. After completion of reaction cool the reaction mixture to 25 C, filtered the precipitated solid and crystallized in methanol to yield compound (2a - l)

2-Amino-4-(4-methoxyphenyl)-6-cyclopropyl-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (2g):

Yield = 78%, M.P=173°C, IR(KBr): ν 2972,2951,2926,2904 (Alkane, -CH str.), 1249(Ar-O-C) cm^{-1} ^{1}H NMR:(DMSO-d_6) δ 0.26 – 0.34 (m, 2H, Cyclopropyl), 0.44 – 0.62 (m, 2H, Cyclopropyl), 1.39 – 1.46(m, 1H, Cyclopropyl), 3.70 (s, 3H, -OCH_3), 4.91 (s,1H, Pyrimidine ring), 6.84 – 7.28 (m, 8H, ArH), 9.10 (s,1H, -SH), 9.32 (s, 1H, -NH) Mass: m/z = 355.3, 234.4, 206.4,M.F. = $C_{20}H_{19}FN_2OS$.

General procedure for the preparation of 4-Aryl-6-cyclopropyl-2-mercapto-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (3a –3l).

A mixture of Chalcones (1a-l) (0.01M) , Guanidine hydrochloride (0.011M) and NaOH (0.022M) in methanol was refluxed with stirring about (6-8 hrs) until complete the reaction. Reaction progress was monitor by TLC. After completion of reaction cool the reaction mixture to 25 C, filtered the precipitated solid and crystallized in methanol to yield compound (2a - l)

4-(4-methoxyphenyl)-6-cyclopropyl-2-mercapto-5-(2'-fluorophenyl)-4,5-dihydropyrimidine (3g):

Yield = 76%, M.P. = 158, IR (KBr): ν 3429, 3317 (-NH_2), 3099,3078,3053,3014, 2955 (Alkane, -CH2), 1286 (-C-N Stretching), 1589 (-N-H Bending), cm^{-1}, ^{1}HNMR: (DMSO-d_6) δ 0.22 – 0.29(m, 1H, Cyclopropyl ring),0.39-0.45 (m,1H, Cyclopropyl ring), 0.75 – 0.78 (m,2H, Cyclopropyl ring), 1.27 – 1.30 (m, 1H, Cyclopropyl ring), 3.72 (s, 3H, -OCH_3), 4.10 (broad, 1H, -NH pyrimidine ring), 5.02 (s, 1H, pyrimidine ring), 5.25 (broad, 2H, -NH_2), 6.77 -7.16 (m, 8H, ArH), Mass: m/z = 338.4 , MF = $C_{20}H_{20}FN_3O$

Characterization data of the compounds 1a-l, 2a-l and 3a-l						
compd no.	Ar	X	Molecular Formula	M.P. (°C)	Nitrogen %	
					Calcd	Found
1a	C_6H_5	--	$C_{18}H_{15}FO$	--	--	--
1b	2Cl C_6H_4	--	$C_{18}H_{14}ClFO$	92	--	--
1c	3Cl C_6H_4	--	$C_{18}H_{14}ClFO$	--	--	--
1d	4Cl C_6H_4	--	$C_{18}H_{14}ClFO$	--	--	--
1e	2,3-diCl C_6H_3	--	$C_{18}H_{13}Cl_2FO$	68	--	--
1f	2F C_6H_4	--	$C_{18}H_{14}F_2O$	--	--	--
1g	4-OCH_3 C_6H_4	--	$C_{19}H_{17}FO_2$	--	--	--
1h	4-CH_3 C_6H_4	--	$C_{19}H_{17}FO$	--	--	--
1i	4-OH C_6H_4	--	$C_{18}H_{15}FO_2$	--	--	--
1j	Thiophene	--	$C_{16}H_{13}FOS$	--	--	--
1k	3-OH C_6H_4	--	$C_{18}H_{15}FO_2$	--	--	--
1l	4-$(CH_3)_2N$ C_6H_4	--	$C_{20}H_{20}FNO$	81	4.53	4.59
2a	C_6H_5	-NH	$C_{19}H_{18}FN_3$	156	13.68	13.75
2b	2Cl C_6H_4	-NH	$C_{19}H_{17}ClFN_3$	178	12.31	12.33
2c	3Cl C_6H_4	-NH	$C_{19}H_{17}ClFN_3$	172	12.31	12.38
2d	4Cl C_6H_4	-NH	$C_{19}H_{17}ClFN_3$	180	12.31	12.22
2e	2,3-diCl C_6H_3	-NH	$C_{19}H_{16}Cl_2FN_3$	185	11.17	11.25
2f	2F C_6H_4	-NH	$C_{19}H_{17}F_2N_3$	152	12.92	12.97
2g	4-OCH_3 C_6H_4	-NH	$C_{20}H_{20}FN_3O$	173	12.46	12.47
2h	4-CH_3 C_6H_4	-NH	$C_{20}H_{20}FN_3$	168	13.08	13.10
2i	4-OH C_6H_4	-NH	$C_{19}H_{18}FN_3O$	193	13.00	13.02
2j	Thiophene	-NH	$C_{17}H_{16}FN_3S$	144	13.41	13.40
2k	3-OH C_6H_4	-NH	$C_{19}H_{18}FN_3O$	191	13.00	12.98
2l	4-$(CH_3)_2N$ C_6H_4	-NH	$C_{21}H_{23}FN_4$	148	16.00	16.02
3a	C_6H_5	-SH	$C_{19}H_{17}FN_2S$	164	8.64	8.66
3b	2Cl C_6H_4	-SH	$C_{19}H_{16}ClFN_2S$	177	7.82	7.80
3c	3Cl C_6H_4	-SH	$C_{19}H_{16}ClFN_2S$	180	7.82	7.82
3d	4Cl C_6H_4	-SH	$C_{19}H_{16}ClFN_2S$	176	7.82	7.83
3e	2,3-diCl C_6H_4	-SH	$C_{19}H_{15}Cl_2FN_2S$	188	7.12	7.13
3f	2F C_6H_4	-SH	$C_{19}H_{16}F_2N_2S$	160	8.18	8.22
3g	4-OCH_3 C_6H_4	-SH	$C_{20}H_{19}FN_2OS$	158	7.91	7.98
3h	4-CH_3 C_6H_4	-SH	$C_{20}H_{19}FN_2S$	155	8.28	8.25
3i	4-OH C_6H_4	-SH	$C_{19}H_{17}FN_2OS$	201	8.23	8.18
3j	Thiophene	-SH	$C_{17}H_{15}FN_2S_2$	168	8.48	8.50
3k	3-OH C_6H_4	-SH	$C_{19}H_{17}FN_2OS$	198	8.23	8.30
3l	4-$(CH_3)_2N$ C_6H_4	-SH	$C_{21}H_{22}FN_3S$	155	11.44	11.38

Table 1

compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	Escherichia coli	Staphylo coccus aureus	Salmonella taphimurium	Bacillus megaterium	Aspergillus niger
1a	09	14	12	10	12
1b	11	21	15	13	18
1c	17	16	14	12	11
1d	15	17	11	16	15
1e	15	12	17	20	10
1f	14	16	22	15	09
1g	19	14	12	13	20
1h	13	11	14	12	13
1i	10	10	18	18	11
1j	20	16	15	11	19
1k	12	21	13	22	14
1l	19	14	20	13	12
2a	12	14	11	15	14
2b	10	12	15	17	14
2c	20	16	13	20	13
2d	14	11	20	17	19
2e	15	22	13	14	15
2f	11	13	14	17	16
2g	14	11	11	15	19
2h	12	19	20	17	10
2i	10	15	15	12	19
2j	23	14	13	26	15
2k	13	11	20	11	11
2l	10	20	12	14	13
3a	18	11	12	09	10
3b	15	17	14	11	18
3c	13	22	12	17	13
3d	20	12	10	15	10
3e	11	14	20	15	11
3f	15	18	14	14	15
3g	13	15	15	19	12
3h	20	13	11	13	19
3i	13	20	20	10	13
3j	14	11	12	20	10
3k	11	15	10	12	18
3l	20	13	23	19	13
Amoxycillin	26	28	27	29	--
Ciprofloxacine	33	34	33	34	--
Chloramphenicol	18	20	19	19	--
Griseofulvin	--	--	--	--	20

Table 2

3. Conclusion

The present study leads to a convenient synthetic method for the synthesis of new Chalcones and pyrimidine derivatives. This showed significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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