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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/18276
DOI URL: http://dx.doi.org/10.21474/IJAR01/18276

RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CHALCONES, PHENYLPYRIMIDINES DERIVATIVES BEARING DIBENZO [b,f][1,4]THIAZEPINES.

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Manuscript Info

Manuscript History
Received: 05 December 2023
Final Accepted: 09 January 2024
Published: February 2024

Key words:-
Chalcones, Phenylpyrimidin, Heterocyclic Compounds, Thiazepine Derivatives, Antimicrobial Activity

Abstract

Chalcones, Phenylpyrimidines derivatives showed remarkable therapeutic activity, with a view of getting to synthesis11-chlorodibenzo[b,f][1,4]thiazepine (1), 1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)ethan-1-one (2),(E)-1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)-3-(4-aryl)prop-2-en-1-ones(3a-3j) &4-substituted-6-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)pyrimidin-2(1H)-ones (4a-4j) have been synthesized, All the synthesized compounds were characterized by TLC, IR, ^{1}H NMR, Mass spectral data. All the synthesized compounds (3a-3j) & (4a-4j) were screened for their antimicrobial activity at 40 µg/ ml concentration.

Introduction:-

Phenylpyrimidines, a class of compounds characterized by a pyrimidine ring structure adorned with a phenyl group, have emerged as intriguing entities in the realm of organic chemistry. Their structural simplicity belies their remarkable versatility and potential applications across various scientific domains.

Phenylpyrimidines have demonstrated noteworthy pharmacological properties, positioning them as promising contenders for drug development. Researchers have delved into their potential for designing and synthesizing compounds with a diverse array of activities, including anti-inflammatory(Ferreira et al., 2023; Goto et al., 2013; Kumar et al., 2017; Sun et al., 2023; Yaddanapudi et al., 2013), anti-cancer(Lee et al., 2021; Rao et al., 2020; Takahashi et al., 2011; Zheng et al., 2022), antimicrobial(Al-Abdullah et al., 2011; Bhadani et al., 2015; Shaban et al., 2000), antiviral(Celik, 2023; Karati, 2022), antibacterial(Al-Abdullah et al., 2011; Bhadani et al., 2015; Karati, 2022; Shaban et al., 2000), anticonvulsant(Aggarwal et al., 2021; Alam, Mullick, et al., 2010; M. R. Ali et al., 2015; Nerkar, 2021; Polish et al., 2020; Shaquiquzzaman et al., 2012; S. Ben Wang et al., 2015), CNS-modulating(Harvey et al., 2006; Lycke et al., 2023; Wostradowski et al., 2016), antihypertensive(Alam, Khan, et al., 2010; K. A. Ali et al., 2011; Farghaly et al., 2019; Irshad et al., 2021; Rani et al., 2016)and analgesic(Antre et al., 2011; Gupta et al., 2012; Sondhi et al., 2005) properties. The distinctive structural characteristics of phenylpyrimidines play a pivotal role in their biological effects, and modifications to their molecular structure can result in amplified or selective activities.

As research progresses in the domains of medicinal chemistry and agrochemicals, phenylpyrimidines are poised to maintain their position as a central focus of interest, owing to their adaptable chemical properties and wide-ranging

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applications. This introduction seeks to offer insight into the importance of phenylpyrimidines in modern chemical research, highlighting their pivotal role in both drug discovery and agricultural advancements.

Chalcones, members of the flavonoid family, encompass both naturally occurring and synthetic compounds. Their defining feature is a distinct chemical arrangement comprising two aromatic rings linked by a three-carbon α,β-unsaturated carbonyl system. The term "chalcone" originates from the Greek "chalcos," meaning bronze, underscoring the yellow hue commonly observed in these substances.

Widely distributed throughout the plant kingdom, chalcones are prevalent in fruits, vegetables, and medicinal flora. They fulfill diverse roles in plant biology, including defense mechanisms against pathogens and pests, as well as contributing to the coloration of flowers and fruits. Owing to their unique structure and varied pharmacological effects, chalcones have garnered significant interest within the realms of medicinal chemistry and pharmaceutical exploration.

The pharmacological properties of chalcones include anti-inflammatory(Chen et al., 2013; Emam et al., 2021; Huang et al., 2020; Li et al., 2017; Mahapatra et al., 2017), antioxidant(Bhatt et al., 2023; Borges et al., 2022; Okolo et al., 2021; Patil et al., 2009), antimicrobial(Henry et al., 2020; Konidala et al., 2021; Narwal et al., 2021), anticancer(Das & Manna, 2016; Elmchichi et al., 2020; Gao et al., 2020; Ouyang et al., 2021; Sunkari et al., 2021), and antiviral(Alaaeldin et al., 2022; Duran et al., 2021; Elkhalifa et al., 2021; Fu et al., 2020; Gan et al., 2017; Y. J. Wang et al., 2018; Zhan et al., 2023) activities.

Different (E)-1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)-3-aryl-prop-2-en-1-one (3a-3j) & 6-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)-4-substituted-pyrimidin-2(1H)-ones (4a-4j) have been synthesized, The structures of the synthesized compounds were assigned based on elemental analysis, TLC, IR, 1H NMR and mass spectral analysis. The antibacterial and antifungal activity was assayed by cup-plate method. All the synthesized compounds evaluated their antibacterial activity against Gram positive bacteria B. subtilis, S. aureus whereas Gram negative bacteria against E. coli, P. aeruginosa. Antifungal activity towards A. Niger antimicrobial activity taken at 40 µg/ ml concentration by cup-plate method. Zone of inhibition in mm.

Antimicrobial activity of synthesized compounds (3a-3j) & (4a-4j) ware compared with known standard drugs e.g. Ampicillin, Chloramphenicol, Norfloxacin and Griseofulvin at some concentration.

Materials and Methods:-

Melting points were taken in open glass capillary tubes are uncorrected. IR spectra (cm-1) were recorded on Shimadzu-435-IR Spectrophotometer and 1H-NMR Spectra on Bruker Spectrometer (400MHz) using TMS as an internal standard, chemical shift in δ ppm.

Synthesis of 11-chlorodibenzo[b,f][1,4]thiazepine (1)

A mixture of dibenzo[b,f][1,4]thiazepin-11-ol; (2.27 gm, 0.01 m); $POCl_3$ (1.51 gm, 0.01 m) was taken. The reaction mixture refluxed for 6 hrs at RT. After completion of reaction the reaction mixture was checked with TLC, the reaction mixture poured into crushed ice, filtered, dried and recrystallization with ethanol.

M.P. 182°C, % yield: 89.24%. Elemental analysis: Required; C, 63.54%; H, 3.28%; N, 5.70%; $C_{13}H_8ClNS$; Found C, 63.01%; H, 3.22%; N, 5.12%.
1H NMR (DMSO): 6.8-8.7 (m, 8, Ar-H)
IR (KBR) (cm^{-1}): 3029 (C-H asym); 1651 (N=C asym), 592 (C-Cl str); 651 (C=C asym)
M/Z: 245, 210, 184, 168 (BP), 154, 137, 122, 108, 90, 76, 60, 46, 35, 32, 26

Synthesis of 1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)ethan-1-one (2)

A mixture of 11-chlorodibenzo[b,f][1,4]thiazepine; (2.45 gm, 0.01 m); 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one (1.66 gm, 0.01 m) was taken. The reaction mixture refluxed for 12 hrs at RT in alkaline condition. After completion of reaction the reaction mixture was checked with TLC, the reaction mixture poured into crushed ice, filtered, dried and recrystallization with ethanol.

M.P. 199°C, % yield: 82.36%. Elemental analysis: Required; C, 70.38%; H, 4.56%; N, 3.73%; $C_{22}H_{17}NO_3S$; Found C, 70.01%; H, 3.32%; N, 3.71%.

1H NMR (DMSO): 2.51 (1, 3H, $COCH_3$); 3.6-4.0 (1, 3H, OCH_3); 6.8-9.1 (m, 17, Ar-H)
IR (KBR) (cm^{-1}): 3052 (C-H asym); 1738 (C=O asym); 1660 (N=C asym); 1284 (C-O str), 702 (C=C asym)
M/Z: 375, 344, 301 (BP), 253, 245, 226, 210, 184, 168, 165, 149, 154, 137, 122, 108, 90, 76, 60, 46, 43, 35, 31, 32, 26

Reaction Scheme

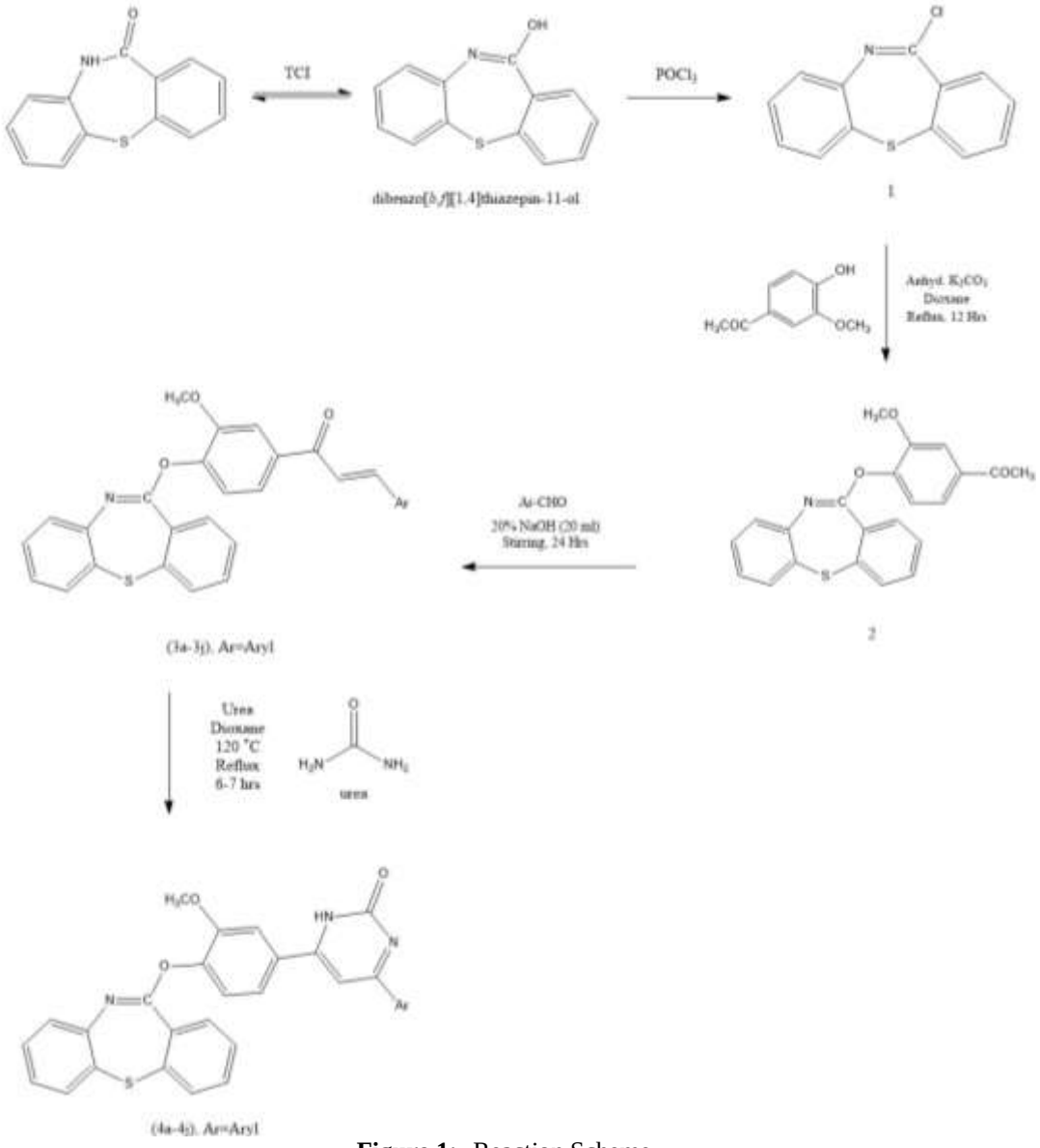

Figure 1:- Reaction Scheme.

Synthesis of (E)-1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one (3g)

A mixture of 1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)ethan-1-one; (3.75 gm, 0.01 m); 2-nitrobenzaldehyde (1.51 gm, 0.01 m) was taken. The reaction mixture refluxed for 24 hrs at RT under alkaline condition. After completion of reaction the reaction mixture was checked with TLC, the reaction mixture poured into crushed ice, filtered, dried and recrystallization with ethanol.

M.P. 192°C, % yield: 83.69%. Elemental analysis: Required; C, 55.64; H, 3.34; N, 9.27; $C_{29}H_{20}N_2O_5S$; Found C, 55.02%; H, 3.18%; N, 9.11%.

1H NMR (DMSO): 3.9 (1, 3H, OCH_3); 7.2-9.1 (m, 17, Ar-H)
IR (KBR) (cm^{-1}): 3062 (C-H asym); 1738 (C=O asym); 1692 (N=C asym); 1521(N-O str); 1251 (C-O str); 673 (C=C asym);
M/Z: 508, 502, 498, 482, 462, 427, 391, 386, 378, 373 (B.P.), 332, 320, 305, 298, 226, 210, 176, 150, 148, 122, 108, 106, 102, 66, 45
Similarly other compounds (3a-3j) have been synthesized.

Synthesis of 4-(2-nitrophenyl)-6-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)pyrimidin-2(1H)-one (4g)

A mixture of (E)-1-(4-(dibenzo[b,f][1,4]thiazepin-11-yloxy)-3-methoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one; (5.08 gm, 0.01 m); urea (0.6 gm, 0.01 m) was taken. The reaction mixture refluxed for 6 hrs at 120°C temperature. After completion of reaction the reaction mixture was checked with TLC, the reaction mixture poured into crushed ice, filtered, dried and recrystallization with ethanol.
M.P. 136°C, % yield: 75.84%. Elemental analysis: Required; C, 70.22; H, 4.38; N, 9.36;$C_{35}H_{26}N_4O_4S$; Found C, 69.98%; H, 4.12%; N, 9.32%.
1H NMR (DMSO); 3.8 (1, 3H, $COCH_3$); 7.0-9.8 (m, 23, Ar-H)
IR (KBR) (cm^{-1}): 3058 (C-H asym); 1720 (C=O asym); 1680 (C=N str); 1648 (N=C asym); 1524 (N-O str); 1261 (C-O str); 672 (C=C asym)
M/Z: 598, 581, 561, 554, 552, 498, 476, 468, 441, 422, 406, 399, 386, 381, 372, 368, 346, 332, 322, 291, 272, 266 (B.P.), 226, 210, 148, 122, 77, 67, 46, 31
Similarly other compounds (4a-4j) have been synthesized.

Table 1:- Physical data of compound (3a-3j).

Sr. No.	Ar	M.F.	M.W.	M.P. (^oC)	% YIELD	% NITROGEN	
						Calculated	Found
3a	C_6H_5-	$C_{29}H_{21}NO_3S$	463.12	187	81.28	3.02	3.05
3b	4-CH_3-C_6H_4-	$C_{30}H_{23}NO_3S$	477.14	176	76.72	2.93	2.99
3c	2-OCH_3-C_6H_4-	$C_{30}H_{23}NO_4S$	493.13	136	81.43	2.84	2.93
3d	4-OCH_3-C_6H_4-	$C_{30}H_{23}NO_4S$	493.13	172	83.30	2.84	2.67
3e	3,4-$(OCH_3)_2$-C_6H_3-	$C_{31}H_{25}NO_5S$	523.15	182	87.76	2.68	2.68
3f	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{32}H_{27}NO_6S$	553.16	175	86.72	2.53	2.40
3g	2-NO_2-C_6H_4-	$C_{29}H_{20}N2O_5S$	508.11	192	83.69	5.51	5.40
3h	3-NO_2-C_6H_4-	$C_{29}H_{20}N_2O_5S$	508.11	138	80.60	5.51	5.62
3i	4-NO_2-C_6H_4-	$C_{29}H_{20}N_2O_5S$	508.11	171	88.35	5.51	5.68
3j	4-NH_2-C_6H_4-	$C_{29}H_{22}N_2O_3S$	478.14	163	84.47	5.85	5.74

Table 2:- Physical data of compound (4a-4j).

Sr. No.	Ar	M.F.	M.W.	M.P. (^oC)	% YIELD	% NITROGEN	
						Calculated	Found
4a	C_6H_5-	$C_{30}H_{21}N_3O_3S$	503.58	146	73.29	8.34	8.26
4b	4-CH_3-C_6H_4-	$C_{31}H_{23}N_3O_3S$	517.6	139	82.38	8.12	8.04
4c	2-OCH_3-C_6H_4-	$C_{31}H_{23}N_3O_4S$	533.6	150	76.36	7.87	7.87
4d	4-OCH_3-C_6H_4-	$C_{31}H_{23}N_3O_4S$	533.6	154	87.32	7.87	8.03
4e	3,4-$(OCH_3)_2$-C_6H_3-	$C_{32}H_{25}N_3O_5S$	563.63	113	83.38	7.46	7.39
4f	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{33}H_{27}N_3O_6S$	593.65	151	86.76	7.08	7.01
4g	2-NO_2-C_6H_4-	$C_{30}H_{20}N_4O_5S$	548.57	136	75.84	10.21	10.32
4h	3-NO_2-C_6H_4	$C_{30}H_{20}N_4O_5S$	548.57	110	74.63	10.21	10.11
4i	4-NO_2-C_6H_4	$C_{30}H_{20}N_4O_5S$	548.57	119	86.58	10.21	10.01
4j	4-NH_2-C_6H_4	$C_{30}H_{22}N_4O_3S$	518.59	132	76.27	10.8	10.91

Antimicrobial Activity

Antimicrobial activity of compounds (3a-3j) & (4a-4j) were taken by cup-plate method(Arthur L. Barry, 1977) whereas Gram positive bacteria B. subtilis, S. aureus and Gram negative bacteria E. coli, P. aeruginosa and antifungal activity were taken by A. niger, all the antimicrobial activity of compounds (3a-3j) & (4a-4j) were compared with known standard drugs. e.g.: Ampicillin, Choramphenicol, Norfloxacin and Griseofulvin at same concentration 40 µg/ ml.

Table 3:- Antimicrobial activity of compounds (3a-3j).

Antimicrobial Activity: (Zone of inhibition in mm)					
Compound No.	**Antibacterial activity**				**Antifungal activity**
	Gram +ve bacteria		**Gram –ve bacteria**		
	B.subtilis	**S.aureus**	**E.coli**	**P.aeruginosa**	**A.Niger**
3a	**17**	**17**	13	**17**	11
3b	14	7	11	13	9
3c	14	14	**16**	15	10
3d	15	9	11	10	14
3e	7	9	17	11	12
3f	11	11	13	9	12
3g	7	11	12	9	**15**
3h	**17**	9	**16**	11	**18**
3i	13	15	14	13	7
3j	11	**18**	14	**18**	9
Ampicillin	**18**	**19**	**13**	**10**	**0**
Chloramphenicol	13	15	15	12	0
Norfloxacin	15	14	12	13	0
Griseofulvin	0	0	0	0	14

Table 4:- Antimicrobial activity of compounds (4a-4j).

Antimicrobial Activity: (Zone of inhibition in mm)					
Compound No.	**Antibacterial activity**				**Antifungal activity**
	Gram +ve bacteria		**Gram –ve bacteria**		
	B.subtilis	**S.aureus**	**E.coli**	**P.aeruginosa**	**A.Niger**
4a	8	7	11	14	**17**
4b	9	**18**	**15**	13	**21**
4c	**19**	**18**	11	**20**	13
4d	14	**21**	**18**	**17**	**19**
4e	**19**	7	10	**19**	11
4f	**21**	**17**	**16**	**19**	**21**
4g	**20**	10	9	10	**21**
4h	**19**	14	10	9	**18**
4i	7	11	8	13	12
4j	12	12	**15**	**19**	**16**
Ampicillin	**18**	**19**	**13**	**10**	**0**
Chloramphenicol	13	15	15	12	0
Norfloxacin	15	14	12	13	0
Griseofulvin	0	0	0	0	14

Results and Discussion:-

Table 5:- Comparable antimicrobial activity of compounds (3a-3j) & (4a-4j).

Antimicrobial Activity: (Zone of inhibition in mm)					
Compound No.	**Antibacterial activity**				**Antifungal activity**
	Gram +ve bacteria		**Gram –ve bacteria**		
	B. subtilis	**S. aureus**	**E. coli**	**P. aeruginosa**	**A. Niger**
3a-3j	3a, 3h	3a, 3j	3c, 3h	3a,3j	3g, 3h
4a-4j	4c, 4e, 4f, 4g, 4f	4b, 4c, 4d, 4e	4b, 4f, 4j	4c, 4d, 4e, 4f, 4j	4a, 4b, 4f, 4g, 4h, 4j

Conclusion:-

The compounds 3a, 3c, 3j, 3j, 4b, 4c, 4d, 4f, 4j showed good antimicrobial activity compared with known standard drugs.

Acknowledgment:-

The authors are thankful to Dr. K. D. Ladva principal and Management of Shri M. & N. Virani Science College (Autonomous), Rajkot for providing research facilities and spectral analysis, also thankful to Head, Department of Chemistry, Saurashtra University, Rajkot for IR, NMR, and Mass spectral analysis. I am grateful to Dr. Neepa Pandhi for screening of antimicrobial activity.

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