International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.5, No.5, pp 2199-2203, July-Sept 2013

Novel one - pot Synthesis and Antimicrobial Activity of 6-chloro-2,4- diphenyl 3,4-dihydro-2H-1,3-benzoxazine derivatives

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Abstract: Novel one - pot synthesis of a series of 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazine derivatives **[2a -2j]** from the reaction of P-Chlorophenol and substituted aromatic aldehyde in methanolic ammonia solution. All synthesized compounds were characterized on the basis of IR,NMR spectroscopic data and Elemental Analysis. Anti-bacterial and Anti-fungal activities were evaluated and compared with the standard drugs, some compounds of the series exhibited promising anti- bacterial and anti- fungal activity compared to standard drugs.
Keywords : Synthesis, Oxazine, Antimicrobial activity.

Introduction:

The development of simple and effective synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Heterocyclic compounds have always been one of the most popular structures in almost every discipline in chemistry[1]. Most of them have diverse biological or medical activities and are very common in natural and non-natural compounds[1].Oxazine and their derivatives are an important class of heterocyclic compounds.. Aromatic oxazines were first synthesized in 1944 by Holly and Cope through Mannich reactions from phenols, formaldehyde, and amines[2]. Oxazine derivatives are played important role in biological and pharamacological field. According to literature survey, Variety of substituted 1,3 oxazine derivatives have been reported claiming diversified biological activities, such as antimicrobial [3-8] and anticoagulant activites [9-10], anticancer [11, 12], fungicidal [13] and anti-tubercular [14-18], ant malarial [19], analgesic, anti-inflammatory [20], antibacterial [21],antidiabetic and hypolipidaemic [22], antiproliferative [23] activites. Owing to the above facts and in continuation of our research work on novel biologically active hetrocycles and their increasing importance in pharamaceuatical and biological field. Therefore, we synthesized new 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazine derivatives using parachlorophenol, aromatic aldehyde in methanolic ammonia and screened their antimicrobial activities.

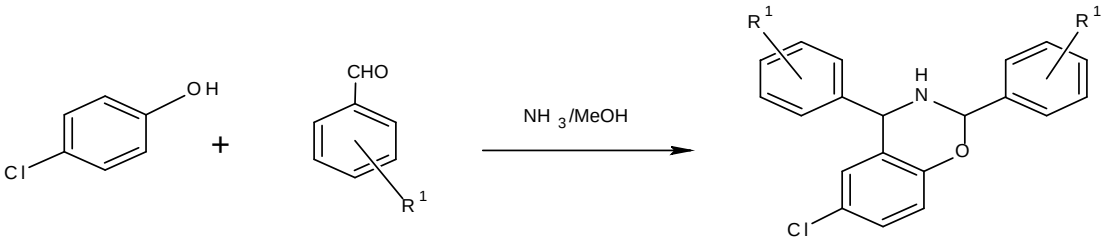
Experimental part:

The melting points were recorded on electro-thermal apparatus and are uncorrected. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminium plates (E Merk) using hexane and ethyl acatate visualized in iodine chamber. IR spectra were recorded in KBr on a perkin-Elmer model-983. 1HNMR spectrum recorded on Varian Mercury 300MHz instrument using $CDCl_3$, DMSO-d_6 as

solvent (chemical shift in δ ppm),using TMS as internal standard. Elemental analysis was performed on a Heracus CHN analyzer and was within the ±0.5% of the theoretical values.

General procedure for preparation of 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxa zine derivatives [2a -2i].

The P-Chlorophenol (0.01 mol) in methanol (10 ml) was added in aromatic aldehyde (0.02 mol; freshly distilled if a liquid) and 10 ml of 25-30% methanolic ammonia. The mixture was left to stand at ambient temperature for 2-3 days, during which the crystalline products separated out. The crude product were filtered off, washed with cold methanol and purified by recrystallization.



[2a -2j]

Table No. 1: Physical and Elemental analysis of Synthesized compounds(2a-2i):

Comp. No.	M.F	R1	M.. W.	M. P. ^{0}C	Yield %	Elemental analysis				
						%C	%H	%N	%O	%Cl
2a	$C_{20}H_{16}ClNO$	C_6H_5	319.9	122	51	74.2	4.9	4.26	4.53	10.7
2b	$C_{22}H_{20}ClNO_3$	4-$OCH_3C_6H_4$	381.1	107	57	69.1	5.1	3.33	12.2	9.15
2c	$C_{20}H_{14}Cl_3NO$	4- ClC_6H_4	388.9	153	75	61.2	3.5	3.2	4.0	27.2
2d	$C_{20}H_{14}Cl_3NO$	2-ClC_6H_4	388.9	169	49	61.3	3.3	3.4	4.10	27.1
2e	$C_{20}H_{16}ClNO_3$	4- OHC_6H_4	353.1	196	55	67.5	4.3	3.64	13.4	9.93
2f	$C_{24}H_{26}ClN_3O$	4.N$(CH_3)_2C_6H_4$	405.3	133	71	70.2	6.1	10.3	3.7	8.49
2g	$C_{20}H_{14}ClN_3O_5$	4- $NO_2C_6H_4$	411.1	113	69	58.3	3.4	10.2	19.3	8.31
2h	$C_{20}H_{14}ClN_3O_5$	2- $NO_2C_6H_4$	411.1	165	61	58.1	3.1	10.2	19.3	8.49
2i	$C_{22}H_{20}ClNO$	4-$CH_3C_6H_4$	349.7	177	53	75.1	5.4	3.78	4.23	10.0

Table No . 2 : Spectral Data of Synthesized Compounds (2a-2i):

Comp No.	IR(KBr) V(cm^{-1})	1H NMR ($CDCl_3$) δ in ppm
2a	3210(N-H),3045 (C-H),1613,1554 (C=C), 775(C-Cl)	5.23(s, CH),6.13(s, CH),6.65-7.85(m, ArH)
2b	3325(N-H),3059 (C-H),1641,1565 (C=C), 778(C-Cl).	5.45(s, CH),6.15(s, CH),6.69-7.87(m, ArH)
2c	3341(N-H),3057 (C-H),1650,1570 (C=C), 778(C-Cl).	5.43(s, CH),6.15(s, CH),6.61-7.80(m, ArH)
2d	3335(N-H),3049 (C-H),1645,1568 (C=C), 777(C-Cl).	5.31(s, CH),6.05(s, CH),6.67-7.73(m, ArH)
2e	3329(N-H),3055 (C-H),1639,1568 (C=C), 775(C-Cl).	5.27(s, CH),6.09(s, CH),6.75-7.67(m, ArH)
2f	3233(N-H),3027(C-H),1665 ,1587 (C=C), 776(C-Cl).	5.21(s, CH),6.10(s, CH),6.67-7.75(m, ArH)
2g	3345(N-H),3063 (C-H),1645,1569 (C=C), 778(C-Cl).	5.61(s, CH),6.19(s, CH),6.65-7.75(m, ArH)
2h	3339(N-H),3056 (C-H),1648,1567 (C=C), 777(C-Cl).	5.41(s, CH),6.17(s, CH),6.64-7.80(m, ArH)
2i	3217(N-H),3047 (C-H),1618,1559 (C=C), 775(C-Cl)	5.25(s, CH),6.13(s, CH),6.65-7.80(m, ArH)

Antimicrobial activity:

The synthesised compounds **(2a-2i)** were screened for their in vitro antimicrobial activity by using cup plate method[25]. Antibacterial activity was screened against two gram positive bacteria *Staphylococcus aureus, Bacillus subtilis* and two gram negative bacteria *Escherichia coli, Pseudomonas aeruginosa* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL. Antifungal activity was screened against *Candida albicans, Aspergillus niger* by measuring the zone of inhibition on agar plates at concentrations 100 µg/mL and reported in Table-3. Nutrient agar was employed as culture medium and DMSO was used as solvent control for antimicrobial activity. Streptomycin and griseofulvin were used as standard for antibacterial and antifungal activities respectively.

Results and Discussion:

The structure of all synthesized compounds are confirmed by IR, 1H NMR spectroscopy. Spectral data are shown in table 2.The compounds were evaluated for their antimicrobial activity. Most of the compounds exhibited good to moderate antitbacterial and antifungal activity against the tested microorganisms. The antibacterial activity are shown in Table 3. The Compound **2b** (R =OCH_3), **2c** (4-Cl),**2d**(2-Cl),**2g**(4-NO_2) showed good activity against various pathogens as compared to standard drug Streptomycin and griseofulvin. The remaining compounds **2a** (R = 4-H), **2e** (4-OH),**2f** (4-N(CH_3), **2h** (2-NO_2), **2i** (4-CH_3) exhibited moderate activities as compared to standard drugs. The antifungal activity are shown in Table 3. The Compounds **2b** (R =4-OCH_3) **2e** (4 –OH), **2f** (4-N(CH_3)$_2$, **2g** (4-NO_2),**2h**(2-NO_2) showed good activity against *Candida albican, Aspergillus niger.* while The remaining compounds (**2a,2c,2d,2i)** exhibited moderate activities as compared to standard drugs. As we consider all results obtained from antibacterial and antifungal tests together we can say that entire compounds tested are active towards bacteria and fungi.

Table No. 3 : Antimicrobial activity of Synthesized Compounds

Comp. (100µg/ml)	Antibacterial				Antifungal	
	S. Aureus	*B. Subtilis*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
2a	09	11	07	05	09	07
2b	15	19	17	09	17	15
2c	16	13	21	17	07	08
2d	14	18	16	17	06	07
2e	09	07	10	05	15	12
2f	06	09	08	12	13	15
2g	15	19	19	18	16	13
2h	07	10	05	09	13	11
2i	11	07	05	08	07	09
Streptomycin	17	20	22	19	-	-
Griesofulvin	-	-	-	-	21	17

Conclusion:

The present work involved the synthesis of series of 6-chloro-2,4-diphenyl-3,4-dihydro-2*H*-1,3-benzoxazine **[2a -2i]** derivatives from P-Chlorophenol and substituted aromatic aldehyde in methanolic ammonia solution, then characterization and *in-vitro* evaluation of antimicrobial activity. All synthesized compounds showed comparable activity.

Acknowledgement:

We are very thankful to the Head Department of Chemistry, Principal Y.C.I.S. Satara for providing laboratory Facilities and Shivaji University Kolhapur, National Chemical Laboratory Pune, for providing necessary instrumental facilities.

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