THE INTERNATIONAL JOURNAL OF SCIENCE & TECHNOLEDGE

Synthesis and Biological Evaluation of Some New Chalcone and Isoxazole Derivatives

Pareshkumar U. Patoliya
Department of Chemistry, Kamani Science College, Amreli, Gujarat, India
Dr. Vipul P. Gohel
Department of Chemistry, Kamani Science College, Amreli, Gujarat, India
Dr. D. M. Purohit
Department of Chemistry, Sree M & N Virani Science college, Rajkot, Gujarat, India
Dr. V. N. Patolia
Department of Chemistry, Kamani Science College, Amreli, Gujarat, India

Abstract:
Some new chalcones and isoxazole derivatives bearing isoindole moiety were prepared. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Key words: *Isoindoline, Chalcone, Isoxazole, 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.

Amongst nitrogen containing five member heterocycles, isoxazoles have proved to be the most useful frame work for biological activities. Isoxazole derivatives have been found to possess a wide range of therapeutic activity such as Antibacterial[12], Anticonvulsant [13], Anticholestermic [14], Anticancer [15], Anthelmintics [16], Antiinflammatory [17], Adenosine antagonist [18], Fungicidal [19], Hypoglycemic [20] and Antiviral [21] etc.

Chalcones and Isoxazole derivatives 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-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl] 3-aryl prop-2-en-1-one (1a–1l) and 3-Aryl-5-[3'-(1",3"-dihydro-1H-isoindol-2"yl)phenyl] isoxazole (2a-l).

The structure of synthesized compounds was assigned based on Elemental analysis, I.R. 1H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method [22] 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-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl] 3-aryl prop-2-en-1-one (1a – 1l) and 3-Aryl-5-[3'-(1",3"-dihydro-1H-isoindol-2"yl)phenyl] isoxazole (2a-l) was carried out in two steps, first by the condensation of 1-(3-(isoindoline-2-yl)phenyl)ethanone (1) 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 hydroxylamine hydrochloride in acetic acid to yield Isoxazole derivatives (2a-l) respectively. (Scheme-1)

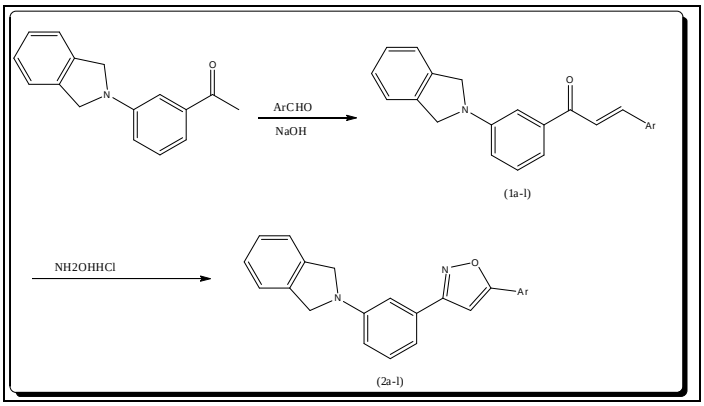
The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR, ^{1}H-NMR, and mass spectral data.

3. Antibacterial Activity

It has been observed from the microbiological data that all compounds (1a-l) and (2a-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 (1g),(1j),(1l),(2c),(2g), (2k) against S.aureus. The significant activity was observed in compounds (1f),(1i),(1l),(2a),(2f) against B. megaterium. The maximum activity was displayed by the compounds (1b),(1d), (1k), (2e), (2i), against E.coli. The compounds (1e), (1i),(1k), and (2l) were comparatively more effective against S. taphimurium.

4. Antifungal Activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (1a),(1g),(1j),(2c),(2f),(2h), 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.



Scheme-1

5. 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-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl] 3-aryl prop-2-en-1-one (1a – 1l):

A mixture of 1-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl]ethanone (1) (0.0211M), aromatic aldehyde (0.0232M) and sodium hydroxide (0.0211M) in methanol was reflux for 6 – 8 hrs and monitors the reaction progress by TLC. After completion of reaction cooled the reaction mixture to 25 – 30°C and filtered the precipitated solid and crystallized in methanol.

(E)-1-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl] 3-(2-chlorophenyl)prop-2-en-1-one (1b):

Yield = 74.5%, M P =193 , IR (KBr): ῡ 3072,3041,3028 Ar-H str ,2928,2874,2845,2839 (Aliphatic –CH str.), 1664 (C=O carbonyl), 1315 (C-N str.) cm^{-1}; ^1H NMR: δ 4.70 (s, 4H, $-CH_2-N-CH_2-$), 6.8 – 7.50 (m, 12H, ArH), 7.76 (s, 1H, -CO-CH=C-), 8.20 (d,1H, -CH=C-CO-); Mass: m/z = 360.2 and 362.1, MF = $C_{23}H_{18}ClNO$.

General procedure for the preparation of 3-(3-(isoindolin-2-yl)phenyl)-5-aryl-4,5-dihydroisoxazole(2a-l):

A mixture of Chalcones (1a-l) (0.01M), Hydroxylamine hydrochloride (0.02M) and sodium acetate (0.022M) in acetic acid was reflux for 6 – 8 hrs and monitors the reaction progress by TLC. After completion of reaction, poured in ice cold water and filtered the precipitated solid and crystallized in methanol.

3-(2-chlorophenyl)-5-[3'-(1",3"-dihydro-1H-isoindol-2"yl)phenyl] isoxazole (2b):

Yield = 74.5%, M P = 187 , IR (KBr): ῡ 3030 (Ar-H str.), 2929, 2856,2825 (Alkane C-H str.), 1604 (Isoxazole C=C str.), 1573 (Isoxazole C=N Str.), 819 (Isoxazole N-O Str.), 750 (C-Cl Str.) cm^{-1} ; ^1H NMR: 4.44 – 4.58 (d, 2H, isoxazole ring), 4.64 (s, 4H, Isoindoline ring), 6.66 – 6.89 (t, 1H, isoxazole ring), 7.19 – 7.91 (m, 12H, ArH); Mass: m/z = 375.1, 377.1 , MF = $C_{23}H_{19}ClN_2O$

compd no.	Ar	Molecular Formula	M.P. (°C)	Nitrogen %	
				Calcd	Found
1a	PhCHO	$C_{23}H_{19}NO$	158	4.30	4.28
1b	2ClPhCHO	$C_{23}H_{18}ClNO$	193	3.89	3.90
1c	3ClPhCHO	$C_{23}H_{18}ClNO$	195	3.89	3.86
1d	4ClPhCHO	$C_{23}H_{18}ClNO$	192	3.89	3.88
1e	2,3-diClPhCHO	$C_{23}H_{17}Cl_2NO$	207	3.55	3.56
1f	2FPhCHO	$C_{23}H_{18}FNO$	178	4.08	4.03
1g	4-OCH_3PhCHO	$C_{24}H_{21}NO_2$	158	3.94	3.96
1h	4-CH_3PhCHO	$C_{24}H_{21}NO$	167	4.13	4.15
1i	4-OHPhCHO	$C_{23}H_{19}NO_2$	221	4.10	4.07
1j	Thiophene	$C_{21}H_{17}NOS$	146	4.23	4.22

1k	3-OHPhCHO	$C_{23}H_{19}NO_2$	225	4.10	4.07
1l	4-$(CH_3)_2$NPhCHO	$C_{25}H_{24}N_2O$	160	7.60	7.63
2a	PhCHO	$C_{23}H_{21}N_3$	174	12.38	12.36
2b	2ClPhCHO	$C_{23}H_{20}ClN_3$	187	11.25	11.24
2c	3ClPhCHO	$C_{23}H_{20}ClN_3$	192	11.25	11.28
2d	4ClPhCHO	$C_{23}H_{20}ClN_3$	185	11.25	11.26
2e	2,3-diClPhCHO	$C_{23}H_{19}Cl_2N_3$	195	10.29	10.30
2f	2FPhCHO	$C_{23}H_{20}FN_3$	166	11.76	11.73
2g	4-OCH_3PhCHO	$C_{24}H_{23}N_3O$	162	11.38	11.37
2h	4-CH_3PhCHO	$C_{24}H_{23}N_3$	179	11.89	11.86
2i	4-OHPhCHO	$C_{23}H_{21}N_3O$	209	11.83	11.81
2j	Thiophene	$C_{21}H_{19}N_3S$	159	12.17	12.19
2k	3-OHPhCHO	$C_{23}H_{20}N_2O_2$	211	7.86	7.82
2l	4-$(CH_3)_2$NPhCHO	$C_{25}H_{25}N_3O$	173	10.96	10.97

Table 1: Physical properties

compd no.	**Antibacterial activity (zone of inhibition in mm)**				**Antifungal activity**
	Escherichia coli	Staphylo coccus aureus	Salmonella taphimurium	Bacillus megaterium	Aspergillus niger
1a	14	09	10	12	18
1b	21	11	13	15	13
1c	16	17	12	14	10
1d	18	15	16	11	11
1e	12	15	20	17	15
1f	16	14	15	22	12
1g	14	19	13	12	19
1h	11	13	12	14	13
1i	10	10	18	18	10
1j	16	20	11	15	18
1k	21	12	22	13	13
1l	14	19	13	20	14
2a	12	11	13	20	14
2b	14	14	16	12	13
2c	13	20	12	13	19
2d	11	12	13	15	15
2e	22	10	16	12	16
2f	13	10	12	16	19
2g	15	19	17	13	10
2h	12	13	15	14	19
2i	24	13	13	11	15
2j	17	12	15	10	11
2k	11	23	14	13	13
2l	14	11	23	15	10
Amoxycillin	26	28	27	29	--
Ciprofloxacine	33	34	33	34	--
Chloramphenicol	18	20	19	19	--
Griseofulvin	--	--	--	--	20

Table 2: Biological activity

6. Conclusion

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

7. Acknowledgment

The authors are thankful to authorities of Kamani Science College, Amreli for providing research facilities and we are also thankful to Department of Chemistry Saurashtra University Rajkot for I.R., N.M.R., Mass spectral & elemental analysis.

8. Reference

1. (a) S. V. Kostanecki and J. Tambor; Chem. Ber., 32, 1921 (1899). (b) B. S. Holla and S. Y. Ambekar; J. Indian Chem. Soc., 50, 673 (1973); Chem. Abstr., 80, 132961 (1974). (c) K. Kazauki, K. Htayama, S. Yokomor and T. Soki; Japan Kokai 75, 140, 429, (Cl. C07 C A61K) 11 Nov. 1975, Appl. 74, 44, 152, 19 Apr. 1974; 4, p.p.; Chem. Abstr. , 85, 5913 (1976).
2. (a) KO, H. H.; Tsao, L. T.; Yu, K. L.; Liu, C. T.; Wang, J. P. and Lin, C. N. Bioorg. Med. Chem., 2003, 11,105. (b) Won, S. J.; Liu C. T.; Tsao, L. T.; Weng, J. R.; Ko, H. H.; Wang J. P. and Lin, C. N. Eur. J. Med. Chem., 2005, 40, 103. (c) Herencia, F.; Ferrandiz, M. L.; Ubeda, A.; Dominguez, J. N.; Charris, J. E.; Lobo, G. M. and Alcaraz, M. J.; Bioorg. Med. Chem. Lett., 1998, 8, 1169.
3. (a) Alkan N. Choudhry and Vijay Juyal; Int J Pharm Pharm Sci, 2011, 3(3), 125. (b) Vesna D. V.; Marina T. M.; Sanda P. D; Zeljko J. V. and Ivan O. J; J. Serb. Chem. Soc., 2012, 77 (6) 741 (c)
4. (a) Wu, X.; Wilairat, P. and Go, M. L. Bioorg. Med. Chem. Lett., 2002, 12, 2299. (b) Mishra, N.; Arora, P. Kumar, B.; Mishra, L. C.; Bhattacharya, A.; Awasthi, S. K. and Bhasin, V. K. Eur. J. Med. Chem., 2007,1.
5. Trivedi, J. C.; Bariwal, J. B.; Dupadhay, K. D.; Naliapara, Y. T.; Joshi, S. K.; Pannecouuque, C.C.; Clerca, E. D. and Shah, A. K.; Tetrahedron Letters., 2007, 48, 8472.
6. Lin, Y. M.; Zhou, Y.; Flavin, M. T.; zhoy, L. M.; Nie, W. and Chen, F. C.; Bioorg. Med. Chem., 2002, 10, 2795.
7. Cabrera, M.; Simoens, M.; Falchi, G.; Lavaggi, M. L.; Piro, O. E.; Castellano, E. E.; Vidal, A.; Azqueta, A.; Monge, A.; Ceran, A. L. D.; Sagrera, G.; Seoane, G.; Cerecetto, H. and Gonzalez, M.; Bioorg. Med. Chem., 2007, 15, 3356.
8. Tomar V.; Bhattacharjee G.; Kamaluddin S.; Srivastava R. K. and Puri S. K.; Eur. J. Med. Chem., 2010, 45(2), 745.
9. (a) A. S. Tomcufak, R. G. Wilkson and R. G. Child; German Patent 2, 502, 490 (1975); Chem. Abstr., 83, 179067 (1975). (b) A. R. Bhatt, R. P. Bhamaria, Mrs. M. R. Patel, R. A. Bellare and C. V. Deliwala; Indian Chem. 10(7), 694 (1972); Chem. Abstr., 78, 119650n (1973).
10. (a) Guo Zongru, Han Rui; CN 1, 13, 909, Chem. Abstr., 125, 103768 (1996). (b) De Vincenzo, R. Seambla G. Panici, P. Benedess, Remelletti F. O.; Anti Cancer Drug Des., 10(6), 481-90 (1995); Chem. Abstr., 124, 247r (1996).
11. (a) Tsotitus Andreas, Kalosorooulou Theodara et al.; PCT Int. Appl., WO 99, 54, 278 (1999); Chem. Abstr., 131, 28260z (1999). (b) Kamei, Hideo, Koide, Tatsurou; Hashimoto Yoko, Kojima et al.; Cancer Biother Radio Pharm. 1997, 12(1), 51-54 (Eng.); Chem. Abstr., 126, 258666v (1997).
12. G. P. Reddy, E. Rajendra and A. K. Murthy; Indian J. Heterocycl., 3, 233 (1994); Chem. Abstr., 122, 105724e (1995).
13. (a) T. Tochiro, K. Shrji, I. Shinji, M. Hiroshi, S. Akira, V. Hiroshi; Gen. Offen. DE, 3, 237,149 (Cl. CO7A 261114) (1983); Chem. Abstr., 99, 88188(1984). (b) T. U. Quazi; Pak. J. Sci. Ind. Res., 27, 326 (1984); Chem. Abstr.,103, 12339m (1985).
14. R. Major, B. Eisele, P. Mutler and H. Grube; Ger. Offen. DE, 3621372 (1988); Chem. Abstr., 108, 67456r (1988).
15. D. R P.Li W. Hwang Chen Shen C. W., C. L Huang c., Chen T. W., J. Med. Chem., 46, 1706 (2003).
16. S. Rung and D. Dus; Pharmazie, 49, 727 (1994); Chem. Abstr., 122, 55934h (1995).
17. (a) Vamanauchi Pharm. Co. Ltd.; Jpn Kokai Koho JP, 58, 148, 858 (Cl. CO7D 207/333) (1982); Chem. Abstr., 100, 34538 (1984). (b) P. T. Gallagher, T. A. Hicka and G. W. Mullier; Eur. Pat. Ep., 2, 57, 882 (1988); Chem. Abstr., 108, 6499K (1988). (c) A. Ando and R. W. Stevens; PCT Int. Appl. WO, 94, 12, 481 (Cl. C07 D 261/04); Chem. Abstr., 122, 56037x (1995). (d) W. Wells, A. Michele, H. Todd, H. Dennis; J. (USA), US Pat. Appl. Publ. US (2002), 49, 213, (Cl. 514-252, 05; C07D 413/02), 25 Apr. 2002, US Appl. PV 209, 6 Jun. 2000, 19 p.p. (Eng.); Chem. Abstr.,136, 340680j (2002).
18. I. A. Shehata and R. A. Glannoh; J. Heterocycl. Chem., 24, 1291 (1987).
19. (a) M. D. Mackie, H. S. Anthony, W. J. R. Howe, S. P. John and W. S. Marry; Brit.; UK Pat. Appl. GB 2, 265, 371 (Cl. C07 D 261/06); Chem. Abstr., 120, 164153z (1994). (b) G. D. Diana and C. P. Michel; S. African ZA, 81, 03, 105 (1981); Chem. Abstr., 98, 1667, (1983). (c) M. Moriyusu, H. Yusui; Gen. Offen. DE, 3, 237,149 (Cl. CO7A 261114) (1983); Chem. Abstr., 99, 88188 (1984).
20. Inai Masatoshi, Tanaka Akie, Goto Kyoto; Jpn Kokai Tokkyo Koho JP, 07, 215, 952 (95, 215, 952) (1995); Chem. Abstr. 124, 86995s (1996).
21. C. P. Alfred, C. David Herman, D. Nancy, B. Daniel; PCT Int. Appl. WO, 95, 22, 9103 (1995); Chem. Abstr., 124, 3055m (1996).
22. (a) A. L. Barry; The antimicrobial susceptibility test: Principle and practices, edited by llluslea & Febiger , (Philadelphia), USA, 180; Biol. Abstr., 1977, 64, 25183. (b) Panda J. Srinivas S. V., Rao M. E.; J. Indian Chem. Soc., 79(9), 770-1 (2002); Chem. Abstr., 138, 153499n (2003)