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Synthesis, Characterization and Biological Evaluation of Some Novel Chalcone Derivatives Containing Imidazo[1,2-a]Pyridine Moiety

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Abstract Chalcone was prepared by the condensation of arylmethyl ketone and arylaldehyde in the presence of alcoholic alkali. Present study describes the synthesis of a series of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*] pyridine-3-yl]-1-substituted arylprop-2-en-1-one compounds (h) 1-9. The compounds were characterized by modern analytical techniques such as CHN analyses, IR, ^{1}H NMR spectra and further supported by mass spectroscopy. All the title compounds were screened for their in vitro antibacterial and antifungal activity against B.coccus, S.aureus, Pseudomona, E.coli, A.niger, Ampicillin, Amoxicillin, Ciprofloxacin, Norfloxacin, Greseofulvin. Their minimum inhibitory concentrations (MIC) were determined. The results of antibacterial activity showed that compounds h 4, h 9 and antifungal activity compounds h 1, h 9 using standard drug.

Keywords: Chalcone, arylmethyl ketone, arylaldehyde, antimicrobial.

INTRODUCTION

The chemistry of chalcones have generated intensive scientific studies throughout the world, specially interesting are their biological and industrial applications. Chalcones are coloured compounds because of presence of the chromophore and auxochromes. They are known as benzalacetophenones or benzylidene acetophenones. Kostanecki and Tambor (1899) gave the name "Chalcone". Chalcones are characterized by their possession of a structure in which two aromatic ring are linked by an aliphatic three carbon chain. The alternative names given to chalcones are phenyl styryl ketones, benzalacetophenone-phenyl acrylphenone, γ-oxo-α-diphenyl-α-propylene and α-phenyl-β-benzoethylene.

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A considerable variety of methods are available for the synthesis of chalcones. The most convenient method is the one that involves the Claisenschimdt condensation of equimolar quantities of an arylmethyl ketone with arylaldehyde in the presence of alcoholic alkali. (Kazauki et al., 1976). Several condensing agents used are alkali of different strength (Rupe and Wasserzug, 1901; Szell, 1959) hydrogen chloride (Lyle and Paradis, 1955; Hemes, 1969), phosphorous oxychloride (Rawal and Shah, 1962), piperidine (Cheng et al., 1963), anhydrous aluminium chloride (Kurodo and Matsukuma, 1932), boron trifluoride (Breslow and Houser, 1940), aq.solution of borax (Jadav and Kulkarni, 1944), amino acids (Reichel, 1944), and perchloric acid (Vlasov, 1972) etc.

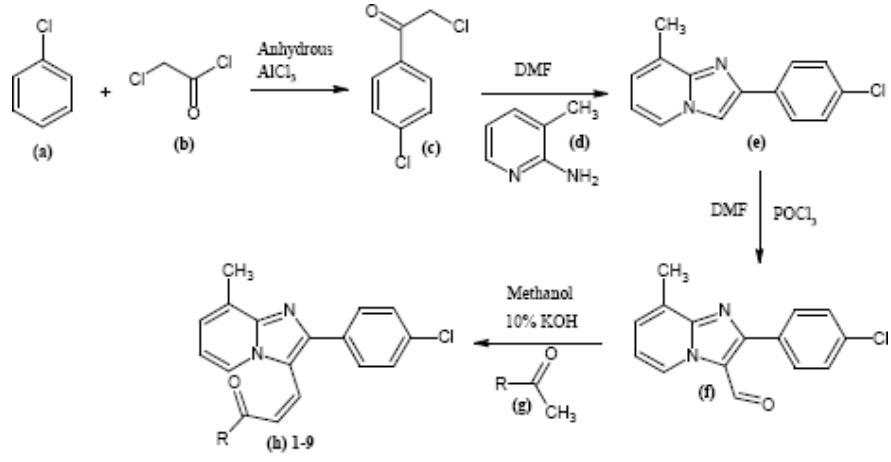
Chalcones are potential biocides, some naturally occurring antibiotics and amino chalcones probably own their biological activity to the presence of α, β - unsaturated carbonyl group. Chalcone derivatives are associated with diverse biological activity. Antiallergic (Ogansyan et al., 1991), Carboxygenase inhibitir (Satoshi et al., 1993), Antitumor (Satomi. 1993, 1994; Auto et al., 1994, 1995), Antimalarial (Li et al., 1995, 1996), Anticancer (Zongru and Rui, 1996), Insecticidal (Nissan Chemical Industries, 1983; Seele R. et al., 1989, 1990), Antiulcer (Tashio Pharmaceutical Co. Ltd., 1984), Antiinflammatory (Serre et al., 1979; Vanstone et al., 1986, 1987), 9. Bactericidal (Bowden et al., 1990, 1991; Inamori et al., 1991, 1991), 10. fungicidal (Gaurav and Ingle, 1986, 1987; Pedersen and Fitz Gerald, 1985), 11. antiviral (Binder et al., 1985), 12. Anthelmintics (Bell, 1984, 1990).

Recently, Ni Liming et al**., (**2002, 2003**)** have synthesized chalcones and screened for their antiinflammatory and cardiovascular activity. Kumar Srinivas et al. (2003) have synthesized chalcones as an antitumor agent. Ko horng-Huey et al. (2003) have prepared chalcones as an antiinflammatory agent. Nakahara Kazuhiko et al. (2003, 2003) have synthesized chalcones as carcinogen inhibitors. Antitubercular agents of chalcone derivatives have been prepared by Lin Yuh-Meei et al. (2002, 2003) Ezico et al. (1999) have demonstrated that chalcone possess a valuable anti-proliferation activity both on sensitive cancereous cell and on cell which are resistant to common chemotherapeutic drugs. Some of the chalcones have been patented for their use for treatment of glueoma (Elichi and Koji, 2000) and showed anti-fungal (Kalashnikov and Kalashnikov, 1994; Satoshi et al., 1993, 1994) aldose reductase inhibitors (Walavalkar and Pednekar, 1999), anticancer (Toru et al., 2000) and antimicrobial (Dimmock and Elisk, 2000;Abdet Rahman, 1998) activities.

MATERIAL AND METHOD

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Waters micromass Q –Tof model instrument. ^1H NMR was determined in $CDCl_3$ solution on a Brucker 400 MHz spectrometer. Elemental analysis of all the synthesized compounds was carried out on Elemental Vario EL III carlo Erba 1108 model and the results are in agreements with the structures assigned.

Reaction Scheme



R = C_6H_5-, 4-CH_3-C_6H_4-, 4-OCH_3-C_6H_4-, 4-Cl-C_6H_4-, 4-F-C_6H_4-, 4-Br-C_6H_4-, 4-NH_2-C_6H_4-, 4-NO_2-C_6H_4-, 4-OH-C_6H_4-

Synthesis of substituted Chalcone derivatives

The product substituted Chalcone derivatives (h) 1-9 has been synthesized by the reaction of aldehyde with different substituted ketone in presence of alcoholic alkali.

General method for the synthesis of (2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-aryl prop-2-en-1-one (h 1-9).

A mixture 2-(4-chlorophenyl)-8-methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (2.70gm,0.01m) and 1-(4-substituted phenyl)ethanone

(1.50gm,0.01m) was refluxed in methanol for 6 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(phenyl)prop-2-en-1-one(h 1).

Yield 59%; M.P. 215 °C; IR (KBr, cm^{-1}): 3066 (aromatic C-H str.), 2918 (alkane asym. C-H str.), 2852 (-CH_3 sym. C-H str.), 1658 (C=O str.), 1645 (CH=CH- str.), 1587 (C=N- str.), 794 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.71 (s, 3H, Ar-CH_3), 7.02-7.95 (d, 8H, Ar-H), 7.45-8.15 (d, 2H, -CH=CH-), 8.48 (d, 1H, -CH=N); MS: m/z 373(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{17}N_2ClO$; Calculated: C, 74.09; H, 4.60; N, 7.51%. Found : C, 74.00; H, 4.56; N, 7.36%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-methylphenyl)prop-2-en-1-one(h 2).

Yield 56%; M.P. 262 °C; IR (KBr, cm^{-1}): 3065 (aromatic C-H str.), 2918 (alkane asym. C-H str.), 2855 (-CH_3 sym. C-H str.), 1655 (C=O str.), 1642 (CH=CH- str.), 1584 (C=N- str.), 796 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.73 (s, 6H, Ar-CH_3), 6.97-8.00 (d, 8H, Ar-H), 7.55-8.20 (d, 2H, -CH=CH-), 8.40 (d, 1H, -CH=N); MS: m/z 387(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{24}H_{19}ClN_2O$; Calculated: C, 74.51; H, 4.95; N, 7.24%. Found : C, 74.36; H, 4.72; N, 7.12%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-methoxylphenyl)prop-2-en-1-one(h 3).

Yield 75%; M.P. 189 °C; IR (KBr, cm^{-1}): 3066 (aromatic C-H str.), 2918 (alkane asym. C-H str.), 2852 (-CH_3 sym. C-H str.), 1658 (C=O str.), 1640 (CH=CH- str.), 1587 (C=N- str.), 795 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.70 (s, 3H, Ar-CH_3), 3.90 (s, 3H, Ar-OCH_3), 6.97-7.95 (d, 8H, Ar-H), 7.55-8.15 (d, 2H, -CH=CH-), 8.43 (d, 1H, -CH=N); MS: m/z 403(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{24}H_{19}ClN_2O_2$; Calculated: C, 71.55; H, 4.75; N, 6.95%. Found : C, 71.63; H, 4.72; N, 6.78%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-chlorophenyl)prop-2-en-1-one(h 4).

Yield 72%; M.P. 185 °C; IR (KBr, cm^{-1}): 3060 (aromatic C-H str.), 2922 (alkane asym. C-H str.), 2850 (-CH_3 sym. C-H str.), 1660 (C=O str.), 1643

(CH=CH- str.), 1590 (C=N- str.), 792 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.75 (s, 3H, Ar-CH_3), 7.00-7.95 (d, 8H, Ar-H), 7.50-8.15 (d, 2H, -CH=CH-), 8.45 (d, 1H, -CH=N); MS: m/z 408(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{16}Cl_2N_2O$; Calculated: C, 67.83; H, 3.96; N, 6.88%. Found : C, 67.88; H, 3.92; N, 6.76%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-fluorophenyl)prop-2-en-1-one(h 5).

Yield 65%; M.P. 140 °C; IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2920 (alkane asym. C-H str.), 2855 (-CH_3 sym. C-H str.), 1658 (C=O str.), 1645 (CH=CH- str.), 1585 (C=N- str.), 1210 (C-F str.), 800 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.72 (s, 3H, Ar-CH_3), 6.95-7.90 (d, 8H, Ar-H), 7.60-8.18 (d, 2H, -CH=CH-), 8.49 (d, 1H, -CH=N); MS: m/z 391(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{16}ClFN_2O$; Calculated: C, 70.68; H, 4.13; N, 7.17%. Found : C, 70.62; H, 4.12; N, 6.98%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-bromophenyl)prop-2-en-1-one(h 6).

Yield 57%; M.P. 243 °C; IR (KBr, cm^{-1}): 3058 (aromatic C-H str.), 2918 (alkane asym. C-H str.), 2856 (-CH_3 sym. C-H str.), 1655 (C=O str.), 1651 (CH=CH- str.), 1589 (C=N- str.), 552 (C-Br str.), 796 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.70 (s, 3H, Ar-CH_3), 7.00-7.95 (d, 8H, Ar-H), 7.55-8.10 (d, 2H, -CH=CH-), 8.44 (d, 1H, -CH=N); MS: m/z 452(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{16}ClBrN_2O$; Calculated: C, 61.15; H, 3.57; N, 6.20%. Found : C, 61.10; H, 3.53; N, 6.15%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-aminophenyl)prop-2-en-1-one(h 7).

Yield 55%; M.P. 165 °C; IR (KBr, cm^{-1}): 3345 (N-H str.), 3060 (aromatic C-H str.), 2915 (alkane asym. C-H str.), 2852 (-CH_3 sym. C-H str.), 1658 (C=O str.), 1649 (CH=CH- str.), 1590 (C=N- str.), 800 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.78 (s, 3H, Ar-CH_3), 6.90-7.00 (d, 8H, Ar-H), 7.62-8.22 (d, 2H, -CH=CH-), 8.49 (d, 1H, -CH=N); MS: m/z 388(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{18}ClN_3O$; Calculated: C, 71.22; H, 4.68; N, 10.83%. Found : C, 71.15; H, 4.66; N, 10.79%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-nitrophenyl)prop-2-en-1-one(h 8).

Yield 70%; M.P. 161 °C; IR (KBr, cm^{-1}): 3066 (aromatic C-H str.), 2920 (alkane asym. C-H str.), 2855 (-CH_3 sym. C-H str.), 1651 (C=O str.), 1644 (CH=CH- str.), 1595 (C=N- str.), 1510 (N-O str.), 796 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ(ppm) 2.75 (s, 3H, Ar-CH_3), 6.97-7.15 (d, 8H, Ar-H), 7.61-8.15 (d, 2H, -CH=CH-), 8.45 (d, 1H, -CH=N); MS: m/z 418(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{16}ClN_3O_3$; Calculated: C, 66.11; H, 3.86; N, 10.06%. Found : C, 66.08; H, 3.83; N, 9.88%.

(2z)-3-[2-(4-chlorophenyl)-8-methylimidazo[1,2-a]pyridine-3-yl]-1-(4-hydroxyphenyl)prop-2-en-1-one(h 9).

Yield 54%; M.P. 149 °C; IR (KBr, cm^{-1}): 3450 (O-H str.), 3062 (aromatic C-H str.), 2915 (alkane asym. C-H str.), 2859 (-CH_3 sym. C-H str.), 1655 (C=O str.), 1640 (CH=CH- str.), 1592 (C=N- str.), 798 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ(ppm) 2.80 (s, 3H, Ar-CH_3), 9.45 (Ar-OH), 6.90-7.30 (d, 8H, Ar-H), 7.55-8.15 (d, 2H, -CH=CH-), 8.50 (d, 1H, -CH=N); MS: m/z 389(M^+), 310, 268, 242, 146, 132; Element Analysis for $C_{23}H_{16}ClN_3O_3$; Calculated: C, 71.04; H, 4.41; N, 7.20%. Found : C, 71.00; H, 4.35; N, 7.04%.

Table 1: Physical data of all synthesized compounds

Sr. No	R	Molecular Formula	Molecular Weight	M.P °C	Rf* Value	% Yield	%Nitrogen	
							Calcd.	Found
h 1	C_6H_5-	$C_{23}H_{17}ClN_2O$	372.5	215.0	0.54	59.0	7.51	7.36
h 2	4-CH_3-C_6H_4-	$C_{24}H_{19}ClN_2O$	386.5	262.0	0.58	56.0	7.24	7.12
h 3	4-OCH_3-C_6H_4-	$C_{24}H_{19}ClN_2O_2$	402.5	189.0	0.60	75.0	6.95	6.78
h 4	4-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_2O$	407.0	185.0	0.59	72.0	6.88	6.76
h 5	4-F-C_6H_4-	$C_{23}H_{16}ClFN_2O$	390.5	140.0	0.44	65.0	7.17	6.98
h 6	4-Br-C_6H_4-	$C_{23}H_{16}ClBrN_2O$	451.5	243.0	0.62	57.0	6.20	6.15
h 7	4-NH_2-C_6H_4-	$C_{23}H_{18}ClN_3O$	387.5	165.0	0.56	55.0	10.83	10.79
h 8	4-NO_2-C_6H_4-	$C_{23}H_{16}ClN_3O_3$	417.5	161.0	0.56	70.0	10.06	9.88
h 9	4-OH-C_6H_4-	$C_{23}H_{17}ClN_2O_2$	388.5	149.0	0.49	54.0	7.20	7.04

Biological Activity

All the compounds have been evaluated for antimicrobial activity using Cup-plate agar diffusion method at a concentration of 40µg using DMF as a solvent against different strains of bacteria and fungi. The antimicrobial activity was compare with standard drug *viz* ciprofloxacin, Amoxicillin, Benzyl-penicillin and antifungal activity was compared with *viz* greseofulvin. The zone of inhibition were measured in mm.

Antibacterial Activity

The purified products were screened for their antimicrobial activity. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B.cocus, S.aureus, Pseudomonas*** and ***E.coli*** in separate conical flask at 40-50°C and mixed well by gentle sacking. About 25ml content of the flask were poured and evenly spreaded in a petridish (13mm in diameter) and allowed to set for 2 hrs. The cups (10mm in diameter) were formed by the help of borar in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.

The plates were incubated at 37°C for 24.0 hrs. and the control was also maintained with 0.04 mole of DMF in a similar manner and the zones of inhibition of bacterial growth were measured in millimeter.

Antifungal Activity

A.Niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Subouraud's agar slants. Steriled Subouraud's agar medium was inoculated with 72 hrs. Old 0.5ml suspension of fungal spores in a separate flask.

About 25ml of inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameters) were punched in petridish and loaded with (0.04g) of solution of sample in DMF. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled with solvent which act as control. The zones of inhibition are recorded in Table 2.

RESULTS AND DISCUSSION

Synthesized all compounds of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*] pyridine-3-yl]-1-(substituted aryl)prop-2-en-1-one starting from chlorobenzene were obtained in good yield. These compounds were characterized on the basis of elemental and spectral analysis.

Table 2: Biological Screening of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-a]pyridine-3-yl]-1-arylprop-2- en-1-one.

Sr. No	R	Zone of Inhibition in m.m.				
		Antibacterial				Antifungal
		B.coccus	S.aureus	Pseudomona	E.coli	A.niger
h 1	C_6H_5-	17	16	13	12	**19**
h 2	4-CH_3-C_6H_4-	15	13	15	14	13
h 3	4-OCH_3-C_6H_4-	16	15	14	15	12
h 4	4-Cl-C_6H_4-	18	**18**	15	16	14
h 5	4-F-C_6H_4-	16	14	15	15	16
h 6	4-Br-C_6H_4-	14	12	13	12	13
h 7	4-NH_2-C_6H_4-	15	14	14	13	15
h 8	4-NO_2-C_6H_4-	13	12	13	14	15
h 9	4-OH-C_6H_4-	**19**	16	**18**	**18**	18
Std^n	Ampicillin	20	19	21	22	-
“	Amoxicillin	22	20	20	21	-
“	Ciprofloxacin	24	23	22	20	-
“	Norfloxacin	23	21	21	22	-
“	Greseofulvin	-	-	-	-	24

IR spectra of each compound showed a band for C=O stretching vibrations near 1650 cm^{-1}, aromatic C-H stretching 3060 cm^{-1}. while primary amine 3350 cm^{-1}, O-H stretching at 3450 cm^{-1}. In case of ^1H NMR shown the chemical shift value of Ar-CH_3 at near 2.70 δ ppm, CH=CH- at near 7.50-8.15 δ ppm . All the title compounds showed [M^+] of 100% intensity as the molecular ion peak. Compound containing chlorine showed isotopic peak at [M+2] of about 33% intensity of that of parent ion peak where as bromo derivative showed isotopic peak at [M+2] of about equal intensity. The results of elemental analyses were found in good agreement with calculated values.

CONCLUSION

Present study describes the synthesis of a series of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-substituted arylprop-2- en-1-one. The compounds were characterized by modern analytical techniques such as C, H, N analyses, IR, Mass and proton NMR spectra. All the title compounds were screened for their in vitro antibacterial and antifungal activity against B.coccus, S.aureus, Pseudomona, E.coli, A.niger, Ampicillin, Amoxicillin, Ciprofloxacin, Norfloxacin, Greseofulvin. Their minimum inhibitory concentrations (MIC) were determined. The results of antibacterial activity showed that compounds h 4, h 9 and antifungal activity compounds h 1, h 9 using standard drug.

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REFERENCES

Abdet Rahman, T. N. (1998) Bull. Chim. Farm.; (2000) Chem. Abstr., **132**, 93276h.

Auto, R. J. et al.(1994) J. Clin. Biochem. Nutr., *17(2)*, 73; (1995) Chem. Abstr., **123**, 122487x.

Bell, M. R. (1984) US Appl., *637*, 931 ; (1990) Chem. Abstr., *113*, 211828t.

Binder, D., Noe, C. R., Holzer, W. and Rosenwirth, B. (1985) Arch. Pharm. **318**(1), 48; (1985) Chem. Abstr., *102*, 149025u.

Bombardelli, E., Piero, V. (1999) PCT Int. Appl. WO 98, 58, 913; Chem. Abstr., **130**, 95382r.

Bowden, K., P., Dal, P. A. and Shah, C. K. (1990) J. Med. Res. Synop., **12**, 2801; (1991) Chem. Abstr., *114*, 160570m.

Breslow, D. S. and Houser, C. R. (1940) J. American Chem. Soc., **62**, 2385; Chem. Abstr., **34**, 7875.

Cheng, P. L., Fournari, P. and Tirouflet, J. (1963) Bull. Soc. Chim. France, 102248; (1964) Chem Abstr., **60**, 1683.

Dimmock, J. R., Elisk, M., U. S. US 6, 017, 933; (2000) Chem. Abstr., **132**, 107880n.

Gaurav, V. M. and Ingle, D. B (1986) Indian J. Chem., **25B**, 86; (1987) Chem. Abstr., **107**, 3932h.

Hemes, S. A. (1969) Chem Abstr., **70**, 96422h.

Inamori, Y. et al. (1991) Chem. Pharm. Bull., **39**(6), 1604; (1991) Chem. Abstr., **115**, 105547c.

Jadav, G. V. and Kulkarni, V. G. (1944) Curr. Sci.

Kalashnikov, B. B., Kalashnikov, I. P. (1994) Chem. Abstr., **130**, 296596n.

Kazauki, K., Htayama, K., Yokomor, S. and Soki, T. (1976) Chem Abstr., **85**, 5913.

Ko Horng-Huey, Tsao Lo- Ti, Yo Kum- Lung, Cheng-Tsung, Wong J. P., Lin C. N. (2003) Bioorg. & Med. Chem., **11**(1), 105-111; (2003) Chem. Abstr., **139**, 30144.

Kostanecki, S. V. and Tambor, J. (1899) Chem. Ber., **32**, 1921. http://dx.doi.org/10.1002/cber.18990320293

Kumar Srinivas, K., Hanger, E., Pehit, C., Gurulingoppal, H., Davidson, N. E., Khan, S. R. (2003) J. Med. Chem., **46**(14), 2813-15; (2003) Chem. Abstr., **139**, 117464.

Kurodo, C. and Matsukuma, T. (1932) Sci. Papers Inst. Phys. Chem. Res. (Tokyo), **18**, 51; (1932) Chem. Abstr., **26**, 2442.

Li Rongshi, Chen. Xiawa., Gong Baogung, Qominguez, Jose N. et al (1995) J. Med. Chem., ***38(26)***, 5031-7; (1996) Chem. Abstr., **124**, 232f.

Lin Yuh-Meei, Zhou Yasheen, Flavin M. T. Zhou L. M. Nie, W., Cheng, F. C. (2002) Bioorg. & Med. Chem., *10(8)*, 2795-2802; (2003) Chem. Abstr., **138**, 66146.

Lyle, R. B. and Paradis, L. P. (1955) J. American Chem. Soc., **77**, 6667; (1956) Chem Abstr., **50**, 10057.

Nakahara Kazuhiko, Torakoontiwakon G., Kaneyama M. , Ono Hiroshi, Yoshida Mitsuru (2003) Jpn. Kokai Tokkyo Koho JP 03, 040829; (2003) Chem. Abstr., **138**, 158753.

Ni Liming, Worsencrott, K. J., Weingarten, M. D., Meng. C. Q., Sikorski, J. A. (2002) U. S. US. WO. 02, 41336; (2003) Chem. Abstr., **139**, 85160.

Nissan Chemical Industries (1983) Chem. Abstr., **98**, 178947a.

Ogansyan, E. T. et al (1991) Khim. Farm. Zh., **25**(8), 18; (1991) Chem. Abstr., 115, 247497n.

Pedersen, A. K. and Fitz Gerald, G. A. (1985) J. Pharm. Sci., **74**(2), 188; (1985) Chem. Abstr., **103**, 87592m.

Rawal, A. A. and Shah, N. M (1962) Indian J. Chem., **21**, 234.

Reichel, L. (1944) Naturwissenschallen, **32**, 215; (1946) Chem. Abstr., **10**, 2441.

Rupe, H. and Wasserzug, D. (1901) Chem Ber., **34**, 3527. http://dx.doi.org/10.1002/cber.19010340342

S. Elichi, S., K. Koji, K. (2000) PCT Int. Appl. WO 99, 61, 403 ; Chem. Abstr., **132**, 12199d.

Satoshi, S., Yasunori, N., Hiroki, V. (1993) J. Med. Chem., 3904-9 (Eng.); (1994) Chem. Abstr., **120**, 133956j.

Satomi, Y. (1993) Ind. J. Cancer, *55(3)*, 506; (1994) Chem. Abstr., **120**, 208071.

Satoshi, S., Yasunori, N., Hiroki, U. (1993) J. Med. Chem., 3904-9 (Eng.); (1994) Chem. Abstr., ***120***, 133956j.

Seele, R. et al. (1989) Eur. Pat. Appl. Ep., *337*, 198(Cl C07D,249/08); (1990) Chem. Abstr., **113**, 178990s.

Serre, H., Rey, J. and Tarayre, J. P. Fr. Demande, 2, *377*, 201 (C1 A 61 K 37/48); (1979) Chem. Abstr., **91**, 9494a.

Szell, T. (1959) Chem Ber., *92*, 1672 ; Chem Abstr., **53**, 21913.

Tashio Pharmaceutical Co. Ltd. (1984) Chem. Abstr., **101**, 54722j.

Toru, O., Yoshihito, O., Shaji, S. (2000) Chem. Abstr., **132**, 22752t.

Vanstone, A. E., Maile, G. K. and Nalbantoglu, L. K. (1986) Ger. Offen., DE 3, **537**, 207(C1. 07c-65/40); (1987) Chem. Abstr., **106**, 49778f.

Vlasov, V. M. (1972) Chem. Abstr., **76**, 40411d.

Walavalkar, P. B., Pednekar, S. (1999) Chem. Abstr., **131**, 257517p.

Zongru, G., Rui, H. (1996) Chem. Abstr., **125**, 10376r.