Journal of Applied Sciences

ISSN 1812-5654

science alert

ANSInet
an open access publisher
http://ansinet.com

Journal of Applied Sciences 7 (12): 1620-1625, 2007
ISSN 1812-5654

Synthetic and Antibacterial Studies of Quinolinylchalcones

Muhammad Azad, Munawar Ali Munawar and Makshoof Athar
Institute of Chemistry, University of the Punjab, Lahore-54590, Pakistan

Abstract: A series of quinolinyl chalcones have been prepared by the condensation of N-substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-ones with different aromatic aldehydes using conventional heating and ultrasound-assisted methods. The percentage yields are considerably increased in ultrasound-assisted method. The prepared chalcone derivatives were assayed for antibacterial and cytotoxicity and were found to be active.

Key words: N-substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-one, chalcone, antibacterial, cytotoxicity, heterocyclic

INTRODUCTION

Quinolines (Meth-Cohn and Narine, 1978; Ali *et al*., 2001) are an important class of heterocyclic compounds and several of their derivatives have been used as bactericidal (Dube *et al*., 1998), anti-inflammatory (Chen *et al*., 2001) and antimalarial (Larsen *et al*., 1996) etc. Many of 4-hydroxy-1,2-dihydro-2-quinolinones have a wide range of applications in pharmacology, i.e., different quinolinones revealed antitumour (Hasegawa *et al*., 1990) anti HSV (Afonso *et al*., 1995), anticonvulsant (Rowly *et al*., 1993), anti-inflammatory (Ukrainets *et al*., 1996) and bactericidal, fungicidal and molluscicidal activity (Mohamed *et al*., 1994). Several 3-substituted quinolin-2(1*H*)-one bearing electron withdrawing groups have been reported to have pharmacological properties. These structures are present in various glycine NMDA receptor antagonists (Hicks *et al*., 1999) and endothelin receptor antagonists (Mederski *et al*., 1997). A few quinolin-2(1*H*)-ones have been used as intermediate in the syntheses of HIV-1 reverse *transcriptase* (Patel *et al*., 2001) inhibitor, 5-HTs receptor antagonists (Anzini *et al*., 1995) and AMPA/Kainate antagonists (Doses *et al*., 1996). Kappe *et al.* (1994) and Stadlbauer and Hojas (2004) have synthesized 3-acetyl-4-hydroxyquinolin-2(1*H*)-one and these compounds have been found to possess anticonvulsant properties (Rowly *et al*., 1993).

Chalcone derivatives belong to another important class of compounds. A large number of chalcone derivatives are found to exhibit antimalarial, antifungal and antibacterial (Katritzky, 1984) and anticancer properties (Rezig *et al*., 2000; Ducki *et al*., 1996). Sayed *et al.* (1976) and Ibrahim *et al.* (1996) have reported the synthesis of a few quinolinyl chalcones using secondary amines as catalyst and acetic acid as solvent.

The use of ultrasonic bath in organic synthesis is well reported, however, the synthesis of chalcones using ultrasonic bath are scarcely reported. The present research involves the comparative study of the synthesis of quinolinyl chalcones under conventional and ultrasound-assisted methods. Antibacterial and cytotoxic study of the prepared chalcones is also the part of this research

MATERIALS AND METHODS

N-ethylaniline, N-methylaniline, diphenylamine, diethylmalonate, 2-nitrobenzaldehyde, 4-chlorobenzaldehyde, benzaldehyde and p-anisaldehyde were purchased from Merck Company and were used as such. ^{1}HNMR and ^{13}CNMR spectra were recorded a Bruker ADVANCE 300 (300.13 MHZ for 1H and 75.5 MHZ for 13C). The NMR spectra were referenced with respect to the non-deuterated residual solvent in the sample. IR spectra were recorded on Perkin Elmer-spectrum. Mass spectra were recorded on a Bruker Esquire 3000+ion trap with ESI ionization. Elemental analyses were performed using Perkin-Elmer 2400-CHN Analyzer. Melting points were recorded on Gallenkamp melting point apparatus and were uncorrected. Ultrasonic bath LC 30 H was used for ultrasonic irradiation. Aluminum coated TLC plates were purchased from Merck company and were used for monitoring of reaction and purity of compounds. N-Substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-ones are prepared by direct fusion of N-substituted anilines and diethyl malonate under Dean Stark trap and are confirmed by comparing the melting points.

General method

Conventional heating method: A mixture of N-substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-one (0.01 mol), aromatic

Corresponding Author: Munawar Ali Munawar, Institute of Chemistry, University of the Punjab, Lahore-54590, Pakistan

aldehyde (0.01 mol), 1-2 drop of piperidine and 1-butanol (25 mL) was refluxed for about 6 h. The precipitates were filtered under suction and washed with cold 1-butanol; dried and crude product was purified by column chromatography and determined the percentage yield.

Ultrasound-assisted method: A mixture of N-substituted-3-acetyl-4-hydroxyquinolin-2(1*H*)-one (0.01 mol), aromatic aldehyde), (0.01 mol), 1-2 drop of piperidine, 1-butanol (5 mL) and 1 g neutral alumina was stirred well for 5 min and removed the solvent under suction. This semi-dried material was heated and irradiated in ultrasonic bath at 60°C for time given in Table 1. TLC monitored the completion of the reaction. The reaction mixture was extracted with chloroform and dried over anhydrous magnesium sulfate and the crude product was purified by column chromatography and determined percentage yield.

4-hydroxy-3-[(*E*)-3-(4-methoxyphenyl)acryloyl]-1-methylquinolin-2(1*H*)-one (2-a): The title compound (2-a) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethylacetate (3:1) as eluent and mp 168-170°C (Lit. m.p. 172-3°C), IR (KBr, ν_{max} in cm^{-1}) 1612 (C = O), 1532 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.53 (d, J = 15.9 Hz, 1 H, H_β), 8.16 (d, J = 7.5 Hz, 1 H, H_5), 7.87 (d, J = 15.9 Hz, 1 H, H_α), 7.59, (m, 3H, H_6, H_7, H_8), 7.19 (m, 2H, H_2', H_6'), 6.86 (m, 2H, H_3', H_5'), 3.81 (s, 3H, OCH_3), 3.53 (s, 3H, N-CH_3). ^{13}CNMR (75.5 MHZ) δ = 193.7 (CO), 176.2, 157.9, 134.5, 131.9, 129.2, 127.9, 126.1, 122.5, 114.2, 55.2, 28.9. Mass spectra (ESI) 336 (M+1, 60%) Anal.$C_{20}H_{17}NO_4$: (335.35): Calcd; C, 71.63; H, 5.11; 4.18; O, 19.08; found: C, 70.98; H, 4.98; N, 4.05%.

4-hydroxy-1-methyl-3-[(*E*)-3-phenylacryloyl)]quinolin-2(1*H*)-one (2-b): The title compound (2-b) was prepared by the reported methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (1:1) as eluent and mp 168-170°C (Lit. m.p. 170-1°C), IR (KBr, ν_{max} in cm^{-1}) 1640 (C = O), 1536 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.6(d, J = 15.9 Hz, 1H, H_β), 8.19 (d, J = 1.8 Hz, 1H, H_5), 7.86 (d, J = 15.9Hz, 1H, H_α), 7.61, (m, 3H, H_6, H_7, H_8), 7.21(m, 3H, H_2', H_4', H_6'), 7.16 (m, 2H, H_3', H_5'), 3.59 (s, 3H, N-CH_3). ^{13}CNMR(75.5 MHZ) δ = 193.1(CO), 176.0, 145.9, 141.6, 135.2, 134.8, 130.6, 129.1, 128.8, 126.3, 125.3, 125.1, 122.2, 114.2, 29.5. Mass spectra (ESI) 306 (M+1, 75%) Anal.$C_{19}H_{15}NO_3$: (305.33): Calcd; C, 74.74; H, 4.95; N, 4.59; O, 15.72; found: C, 73.9; H, 4.86; N, 4.35%.

3-[(*E*)-3-(4-chlorophenyl)acryloyl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (2-c): The title compound (2-c) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (3:1) as eluent and mp 182-184 ^{0}C, IR (KBr, ν_{max} in cm^{-1}) 1644.7 (C = O), 1536.6 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.5(d, J = 15.6 Hz, 1H, H_β), 8.2 (d, J = 8.5 Hz, 1H, H_5), 7.8 (br-m, 4H, H_α, H_6, H_7, H_8), 7.5, (m, 4H, protons of chlorophenyl), 3.2 (s, 3H, N-CH_3). Mass spectra (ESI) 340 (M+1, 60%) Anal.$C_{19}H_{14}ClNO_3$: (339.77): Calcd; C, 67.16; H, 4.15; N, 4.12;Cl, 10.43; O, 14.13; found: C, 66.9; H, 4.00; N, 3.98%.

Table 1: Prepared quinolinylchalcones under different heating methods

Compound	Conventional time (h) of reflux	Yield (%)	Ultrasound-assisted time (min) at 60°C	Yield (%)
2-a	6	36	70	68
2-b	6	38	85	74
2-c	6	26	80	72
2-d	6	35	80	74
2-e	6	27	85	65
2-f	6	32	90	68
2-g	6	28	85	65
2-h	6	28	80	63
2-I	6	36	90	75

4-hydroxy-1-methyl-3-[(*E*)-3-(2-nitrophenyl) acryloyl]quinolin-2(1*H*)-one (2-d): The title compound (2-d) was prepared by the reported methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (1:1) as eluent and mp 202-204°C (Lit. m.p. 163°C), IR (KBr, ν_{max} in cm^{-1}) 1632 (C = O), 1529.5 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.58(d, J = 15.6 Hz, 1H, H_β), 8.24 (d, J = 7.8 Hz, 1H, H_5), 7.94 (d, J = 15.6 Hz, 1H, H_α), 7.67, (m, 3H, H_6, H_7, H_8), 7.26 (m, 2H, H_3', H_5'), 6.92(m, 2H, H_2', H_4'), 3.84 (s, 3H, N-CH_3). ^{13}CNMR(75.5 MHZ) δ =194.13 (CO), 176.2, 161.92, 161.42, 145.27, 140.72, 13.7, 131.0, 128.0, 126.4, 122.7, 121.8, 116.5, 114.3, 114.0, 105.4, 55.4 Mass spectra (ESI). (351, M+1, 65%) Anal.$C_{19}H_{14}N_2O_4$: (350.32): Calcd; C, 65.14; H, 4.03; N, 8.00; O, 22.84; found: C, 65.23; H, 3.96; N, 8.12%.

3-[(*E*)-3-(4-chlorophenyl)acryloyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (2-e): The title compound (2-e) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (1:1) as eluent and mp 166-168°C, IR (KBr, ν_{max} in cm^{-1}) 1614.2 (C = O), 1538.1 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.57(d, J = 15.6 Hz, 1H, H_β), 8.17 (d, J = 8.1 Hz, 1H, H_5), 7.78 (d, J = 15.6 Hz, 1H, H_α), 7.6, (m, 3H, H_6, H_7, H_8), 7.28 (br-m, 4H, protons of chlorophenyl), 4.2(q, 2H, N-CH_2), 1.3 (t, 3H, proton of CH_3) ^{13}CNMR(75.5 MHZ) δ = 194.2(CO), 176.0, 161.3, 143.2, 140.0, 136.4, 134.9, 133.7, 130.1, 129.1, 126.4, 125.8, 121.9, 116.2, 114.1, 105.6, 37.2, 12.8. Mass spectra (ESI) 354(M+1, 100%), 356(M+1+2, 33%) Anal.$C_{20}H_{16}ClNO_3$: (353.8): Calcd; C, 67.9; H, 4.56; N, 3.96; Cl, 10.02; O, 13.57; found: C, 67.54; H, 4.48; N, 3.92%.

1-ethyl-4-hydroxy-3-[(*E*)-3-phenylacryloyl]quinolin-2(1*H*)-one (2-f): The title compound (2-f) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (2:1) as eluent and mp 132-134°C (Lit. m.p. 135-6°C), IR (KBr, ν_{max} in cm^{-1}) 1615.2 (C = O), 1536.9 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.6(d, J = 15.6 Hz, 1H, H_β), 8.19 (d, J = 9 Hz, 1H, H_5), 7.9 (d, J = 15.6 Hz, 1H H_α), 7.64, (br-m, 3H, H_6, H_7, H_8), 7.39 (m, 3H, H_2', H_4' H_6'), 7.23 (m, 2H, H_3', H_5'), 4.2 (q, 2H, N-CH_2), 1.34 (t, 3H, proton of CH_3) ^{13}CNMR (75.5 MHZ) δ = 194.2 (CO), 176.2, 161.2, 144.9, 140.6, 135.2, 134.8, 130.6, 129.6, 129.0, 128.9, 128.6, 126.4, 125.2, 125.0, 121.9, 116.2, 114.0, 105.4, 37.2, 12.8 Mass spectra (ESI) 320 (M+1, 100%) Anal.$C_{20}H_{17}NO_3$: (319.35): Calcd; C, 75.22; H, 5.37; N, 4.39; O, 15.03; found: C, 74.95; H, 5.42; N, 4.23%.

4-hydroxy-3-[(*E*)-3-(4-methoxyphenyl)acryloyl]-1-phenylquinolin-2(1*H*)-one (2-g): The title compound (2-g) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (3:1) as eluent and mp 262-264°C (Lit. m.p. 260°C), IR (KBr, ν_{max} in cm^{-1}) 1648 (C = O), 1568 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.52(d, J = 15.6 Hz, 1H, H_β), 8.24 (d, J = 8.1 Hz, 1H, H_5), 7.94 (d, J = 15.6 Hz, 1H, H_α), 7.54, (br-m, 5H, H_6, H_7, H_8, H_2', H_6'), 7.43 (br-m, 3H, H_3', H_4' H_5'), 7.19 (m, 4H, protons of 4-methoxyphenyl), 3.8(s, 3H, protons of OCH_3). Mass spectra (ESI) 398 (M+1, 65%) Anal.$C_{25}H_{19}NO_4$: (412.46): Calcd; C, 75.55; H, 4.82; N, 3.52; O, 16.10; found: C, 76.42; H, 4.68; N, 3.82%.

4-hydroxy-1-phenyl-3-[(*E*)-3-phenylacryloyl]quinolin-2(1*H*)-one (2-h): The title compound (2-h) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (4:1) as eluent and mp 282-284°C (Lit. m.p. 306-10°C), IR (KBr, ν_{max} in cm^{-1}) 1660 (C = O), 1536.9 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.3(d, J = 15.6 Hz, 1H, H_β), 8.26 (d, J = 8.1 Hz, 1H, H_5), 7.96 (d, J = 15.6 Hz, 1H, H_α), 7.8-7.4, (br-m, 6H, H_6, H_7, H_8, H_2', H_4', H_6'), 7.3-7.0 (br-m, 7H, H_3', H_5'and 5H of phenyl ring), Mass spectra (ESI) 368 (M+1, 100%) Anal. $C_{24}H_{17}NO_3$: (367.4): Calcd; C, 78.46; H, 4.66; N, 3.81; O, 13.06; found: C, 78.34; H, 4.48; N, 3.62%.

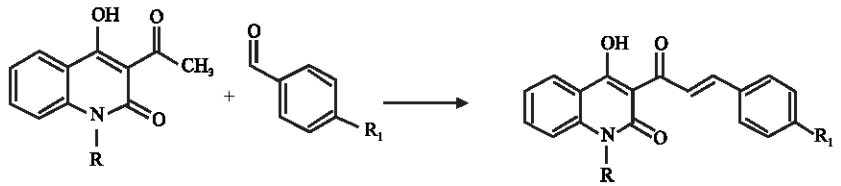
3-[(*E*)-3-(4-chlorophenyl)acryloyl]-4-hydroxy-1-phenylquinolin-2(1*H*)-one (2-I): The title compound (2-I) was prepared by the described methods and purified by column with the mixture of solvents n-hexane: ethyl acetate (3:1) as eluent and mp 240-242°C, IR (KBr, ν_{max} in cm^{-1}) 1648 (C = O), 1536.9 (C = C), ^{1}HNMR (300 MHZ, $CDCl_3$) δ = 8.62 (d, J = 15.6 Hz, 1H, H_β), 8.29 (d, J = 1.2 Hz, 1H, H_5), 7.89 (d, J = 15.6 Hz, 1H, H_α), 7.65 (m, 5H, protons of N-phenyl), 7.48 (m, 2H, H_6, H_7), 7.43 (m, 5H, H8, 4 protons of p-chlorophenyl). Mass spectra (ESI) 402 (M+1, 100) Anal.$C_{24}H_{16}ClNO_3$: (353.8): Calcd; C, 71.73; H, 4.01; N, 3.49; Cl, 8.82; O, 11.94; found: C, 72.06; H, 3.95; N, 3.32%.

RESULTS AND DISCUSSION

The present study was aimed to prepare the quinoline-based chalcone derivatives by using both conventional and ultrasound-assisted methods. Both the methods are compared with reference to reaction time, temperature and percentage yields. The chalcone derivatives are prepared by the condensation of N-substituted-3-acetyl-4-hydroxyquinolin-2(1H)-ones with different aromatic aldehydes using piperidine as catalyst in 1-butanol, as there was no reaction in alcoholic sodium/potassium hydroxide (Scheme 1).

By the use of ultrasound-assisted method, reaction time is reduced marvelously from 6.0 h to 70-90 min and product yields are increased approximately two folds. Energetically preparation of quinolinyl chalcone derivatives by using ultrasound assisted method is more feasible than conventional heating (Table 1). Li *et al.* (2002) have reported similar results in the formation of simple chalcones by using pulverized KOH and KF-Al_2O_3. The product yields of chalcone derivatives probably increased due to decrease in Cannizzaro reaction. The optimum temperature in case of ultrasonic irradiation is found to be 60°C and results obtained are given in Table 1.

The structures of all the synthesized quinolinyl chalcone derivatives have been confirmed by their spectroscopic data such as IR, ^{1}HNMR, ^{13}CNMR, Mass



Scheme 1

Table 2: Antibacterial activity of newly synthesized chalcones

	Antibacterial activity of chalcones zone inhibition (mm)														
	Gram positive									Gram negative					
	Staphylococci Conc. (mg mL^{-1})			*B-megtesium*-1 Conc. (mg mL^{-1})			*Escherichia coli* Conc. (mg mL^{-1})			*Salmonella typhi* Conc. (mg mL^{-1})			*Proteus vulgaris* Conc. (mg mL^{-1})		
Compound	33	66	100	33	66	100	33	66	100	33	66	100	33	66	100
2-a	9	9	10	7	8	10	8	9	11	5	7	8	8	9	10
2-b	10	11	12	9	9	10	12	13	14	8	8	10	9	10	10
2-c	15	16	17	15	16	18	14	14	16	10	12	13	13	15	15
2-d	15	16	16	12	13	13	11	12	14	12	12	13	13	15	16
2-e	16	16	17	14	14	16	12	15	16	14	14	16	14	16	16
2-f	15	16	16	12	10	11	11	9	10	11	12	13	14	15	15
2-g	8	8	9	7	8	10	6	6	8	10	10	11	9	11	12
2-h	10	12	13	9	10	11	7	9	9	12	12	13	10	10	12
2-I	13	14	16	11	11	12	13	14	16	14	15	16	12	12	14
Strep.	18	18	20	12	12	12	15	16	18	17	18	20	14	16	20

and CHN analyses. It is remarkable to note that in ^{1}HNMR spectra of all the described compounds, α,β unsaturated enone system protons have appeared as two doublets around δ 8.6 ppm and δ 7.8 ppm for H_{β} and H_{α}, respectively, with coupling constant between 15-16 Hz. The coupling constants predict that chalcone derivatives are trans isomers. The other peaks have appeared in the expected region and the numbers of protons are in accordance with the expected protons. Additional support to elucidate the structures is obtained from ^{13}CNMR spectra of these compounds. The appearance of peak around δ 194 ppm indicates the α, β unsaturated carbonyl carbon present in the chalcones. M+1 peak in mass spectra (ESI) is the promising peak in most of the described compounds.

Some prepared compounds have long range of difference in their melting points with the literature melting points (Sayed *et al*., 1976; Ibrahim *et al*., 1996). The reported compounds have been supported only by CHN analyses. The compounds described in this study have been supported by spectroscopic data as well as CHN analyses.

Antibacterial activity of prepared quinolinyl chalcones: All the prepared chalcones were screened for their antibacterial activities against the following four organisms *viz*., *Staphylococci*, *Bacillus megtesium*-1, *Salmonella typhi*, *Escherichia coli* and *proteus vulgaris*. For preliminary screening the antibacterial tests were carried out by using disc diffusion method (Karaman *et al*., 2003). One hundred microlitres of suspension containing 10^{8} colony forming unit (CFU mL^{-1}) of bacteria were spread on Mueller-Hinton agar (MHA) medium. The discs (6 mm in diameter), impregnated with 10 μL of the test compounds of different concentrations (33, 66 and 100 mg mL^{-1}) were placed on the inoculated discs. Negative controls were prepared by using the same solvent chloroform ($CHCl_3$), employed to dissolve the test compounds. Streptomycin 10 μL (33, 66 and 100 mg mL^{-1}) was used as positive reference standard to determine the sensitivity of each bacterial species tested. The discs were placed into the medium containing plates incubated at 37°C for 24 h. Antibacterial activity was evaluated by measuring the diameter (mm) of zone of inhibition around each disc and results were recorded in Table 2.

On the basis of the observed zone inhibition values, it is well understood that all the prepared chalcones have shown antibacterial activity against both the gram-positive and gram-negative bacterial strains. These prepared chalcone derivatives have inhibited the bacterial strains significantly.

Preliminary cytotoxic evaluation of chalcones: All the synthesized quinolinyl chalcone derivatives were evaluated *in vitro* against three-cell line panel consisting of MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS). In this protocol, each cell line was inoculated and pre-incubated on a microtiter plate. Test agents were then added at a single concentration (100 μM) and the culture incubated for 48 h. End-point determinations were made with alamar blue (Gray and Wickstrom, 1996). Results for each test agent were recorded as the percent growth of the treated cells when compared to the untreated control. Compounds, which reduced the growth of any one of the cell lines to 32% or less, were considered to be cytotoxic.

According to the above-described criteria, chalcone derivatives 2-c, 2-e and 2-I are found to possess significantly high cytotoxicity, however, other chalcone derivatives have shown moderate cytotoxicity (Table 3).

Table 3: Cytotoxicity of quinolinyl chalcones

Compound	MCF7 (Breast cancer)	NCI-H460 (Lung cancer)	SF-268 (CNS cancer)
2-a	31	21	27
2-b	22	23	19
2-c	15	12	16
2-d	25	17	29
2-e	18	14	28
2-f	23	27	34
2-g	36	38	46
2-h	28	24	26
2-I	13	18	11

ACKNOWLEDGMENT

The authors acknowledge the enabling role of the Higher Education Commission Islamabad, Pakistan and appreciate its financial support through Development of S and T Manpower through Indigenous Ph.D and we are also thankful to Prof. Dr. Paul W. Groundwater, Sunderland Pharmacy School University of Sunderland SR_1 3SD UK for the spectral measurements.

REFERENCES

Afonso, A., J. Weinstein and M.J. Gentles, 1995. U.S. US 5,382,572, 1995; Prepration of alkyl and acyl substituted quinolinesas antiviral agents. Chem. Abstr., 122: 213949r.

Ali, M., M. Tasneem, K.C. Rajanna and P.K. Saiprakash, 2001. An efficient and facile synthesis of 2-chloro-3-formylquinolines from acetanilides in miceller by Vilsmeier Haack cyclisation. Synlet., 2: 251-253.

Anzini, M., A. Cappelli, S. Vomero, G. Giorge, T. Langer, M. Hamoon, N. Merahi, B.M. Emerit, A. Cagnotto, M. Skorupska, T. Mennini and J.C. Pinto, 1995. Novel, potent and selective 5-HTZ receptor antagonists based on the piperizine skelton: Synthesis, structure biological activity and comparative molecular field analysis. J. Med. Chem., 38: 2692-2704.

Chen, Y.L., K.C. Fang, J.Y. Sheu, S.L. Hsu and C.C. Tzeng, 2001. Synthesis and antibacterial evaluation of certain quinolone derivatives. J. Med. Chem., 44: 2374-2377.

Doses, P., J.M. Lepagnol, P. Morain, P. Lestage and A.A. Cordi, 1996. Structure-Activity relationship in a series of 2(1*H*)-quinolones bearing different acidic function in the 3-position: 6,7-dichloro-2(1*H*) oxoquinoine-3-phosphonic acid, a new potent and selective AMPA/Kainate Antagonist with Neuroprotective properties. J. Med. Chem., 39: 197-206.

Dube, D.M. Bloun, C. Brideau, C. Chan, S. Desmarais, D. Eithier, J.P. Falgueyeret, R.W. Friesen, M. Girad, Y. Girad, J. Guay, P. Tagri and R.N. Yong, 1998. Quinolines as potent 5-lipoxygenase inhibitor: Synthesis andbiological profile. Bioorg. Med. Chem. Lett., 8: 1255-1260.

Ducki, S., J.A. Hadfield, N.J. Lawerence and X. Zhang, 1996. Isolation of E-1-(4-hydroxy phenyl)-but-1-en-3-one from *Scutellaria barbata*. Planta Medica, 62: 185-186.

Gray, G.D. and E. Wickstrom, 1996. Evaluation of Anchorage-Indepdent proliferation in Tumorigenic cells using the redox dye alamar blue. Biotechniques, 21: 780-782.

Hasegawa, S., K. Masunaga, M. Muto and S. Hanada, 1991. Jpn. Tokkyo Koho JP 02 32,086[9032,086], 1990. Platinium compound and agent for treating malignant tumor. Chem. Abstr., 114: 34897k.

Hicks, C.A., M.A. Ward, N. Ragumorthy, S.A. Amber, C.P. Dell, D. Dobson, J.M. O'Neil, 1999. Evaluation of glycine site antagonists vof the NMDA receptor in global cerebral ischaemia. Brain Res., 819: 65-74.

Ibrahim, S.S., H.A. Allimony and E.S. Othman, 1996. 3-Acryolyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo quinoline derivatives and their behaviour towards some nucleophiles. Chem. Papers, 51: 33-42.

Kappe, T., R. Aiger, P. Hohengassner and W. Stadlbauer, 1994. Synthesis of 3-Acyl-4-hydroxy-2(1*H*) quinolones. J. Parkat. Chem., 336: 596-601.

Karaman, I., F. Sahin, M. Gulluce, H. Ogutcu, M. Sengul and Adiguzel, 2003. Antimicrobial activity of aqueous and methanol extracts of *Junipreus oxycedrus* L. J. Ethnopharmacol., 85: 231-235.

Katritzky, A.R., 1984. Comprehensive Hetrocyclic Chemistry. Rees, C.W. (Ed.), Vol. 2. Pergamon Press, Oxford.

Larsen, R.D., E.G. Corley, A.O. King, J.D. Carrol, P. Davis, T.R. Verhoeven, P.J. Reider, M. Labelle, J.Y. Gauthier, Y.B. Xiang and R. Zamboni, 1996. Practicalroute toa new class of LTD_4 Receptor Antagonists. J. Org. Chem., 61: 3398-3405.

Li, J.T., W.Z. Yang, S.X. Wang, S.H. Li and T.S. Li, 2002. Improved synthesis of chalcones under ultrasonic irradiation. Ultrason Sonochem., 9: 237-239.

Mederski, W.W., M. Oswald, D. Dorsch, M. Christlader, C.J. Schmitges and C. Wilm, 1997. 1,4-Diaryl-2-oxo-1,2-dihydroquinolin-3-carboxylic acid as endothelin receptor antagonists. Bioorg. Med. Chem. Lett., 7: 1883-1886.

Meth-Cohn, O. and B. Narine, 1978. A versatile new synthesis of quinolines, thiopyrimidines and related fused pyridines. Tetrahedron Lett., 23: 2045-2048.

Mohamed, E.A., M.M. Ismil, Y. Gabr and M. Abass, 1994. Synthesis of some multiazaheterocycles as substituents to quinolone moiety of specific biological activity. Chem. Papers, 48: 285-292.

Patel, M., R.J. Mc Hugh, B.C. Cordova, R.M. Klabe, L.T. Bachler, S. Erikson-Viitanen and J.D. Rodgers, 2001. Synthesis and evaluation of novel quinolines as HIV-reverse transcriptase inhibitors. Bioorg. Med. Chem. Lett., 11: 1943-1945.

Rezig, R., M. Chebah, S. Rhouati, S. Ducki and N.J. Lawrence, 2000. Synthesis of some quinolinyl aryl unsaturated ketones. J. Soc. Alger. Chim., 10: 111-120.

Rowley, M., P.D. Leeson, G.I. Stevenson, A.M. Moseley, I. Stansfield, I. Sanderson, L. Robinson, R. Baker, J.A. Kemp, Marshell, A.C. Foster, S. Grimwood, M.D. Tricklebank and K.L. Saywell, 1993. 3-acyl-4-hydroxyquinolin-2(1*H*)-ones.- Systematically active anticonvulsants action by antagonism at the glycine site of N-methyl-D-asparate receptor complex. J. Med. Chem., 36: 3386-3396.

Sayed, A.A., S.M. Sami, A. Elfayoumi and E.A. Mohamed, 1976. The behaviour of some 3-substituted 4-hydroxy-1-alkyl (or phenyl) carbostyrils towards amines and hydrazines. Egypt J. Chem., 19: 811-826.

Stadlbauer, W. and G. Hojas, 2004. Ring closure reactions of 3-arylhydrazonalkyl-quinolin-2-ones to 1- aryl-pyrazolo[4,3-C]quinolin-2-ones. J. Heterocyclic Chem., 41: 681-690.

Ukrainets, I.V., S.G. Taran, L.V. Sidorenko, O.V. Gorokhova, A.A. Ogirenko, A.V. Turov and N.I. Filimonova, 1996. 4-Hydroxy-2-quinolones. 31. 3-amino-IR-2-oxop-4=hydroxyquinolines and their acyl derivatives. Khim. Geterotsikl. Soedin., 8: 1113-1123.