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RESEARCH ARTICLE

Studies on synthesis of quinolinylchalcones as a new class of Anti-microbial agents.

Vivek S. Patel[1], Mayank S. Patel[2], Divyanshu D. Patel[3], Dr.P.S.Patel[a], Prof. K.C.Patel[b]

1. Department of chemistry, Narmada College of Science and Commerce, Zareshwar. Bharuch, India

2. Department of Chemistry Veer Narmad South Gujarat University, Surat, India

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Corresponding Author

Vivek S. Patel

Abstract

A series of quinolinyl chalcones were prepared by Claisen-Schmidt condensation with formylquinonyl and different aromatic acetophenone in presence of aqueous NaOH and methanol at room temperature. The newly synthesized compounds have been characterized by IR and ^{1}H NMR. All the new compounds were evaluated for their antibacterial and antifungal activities.

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Introduction

An interesting feature of chalcones is that they serve as starting materials for the synthesis of another class of naturally occurring and widely distributed pigments called flavones. In present work, 2-chloro-5,7-difluoroquinoline-3-carbaldeyde intermediate was prepared by using Vilsmeir-Haack reagent, phosphorus oxy chloride and dimethylformamide (Meth-Cohn., et al 1981). Synthesis of the title compound based on Claisen-Schmidt condensation (Abdullah et al., 2009),(Gupta et al., 2010),(Rizvi et al., 2010),(Patel et al., 2013), (Dave et al., 2009).The presence of a reactive α, β unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity. Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications.

In the present study, the quinoline nucleus and chalcone functionality have been incorporated in a single molecule and deliberated their antimicrobial (Buzzi et al., 2007) and antileishmanial (Nielsen et al., 1998) activities with variation of substituent at different positions in the aromatic ring. Quinoline-based chalcones have been reported to possess antimalarialactivity (Chen et al., 1997). Chalcones as well as some quinoline derivatives have already been recognized for their antileishmanial activities. Chalcones have been used as anti HIV agents (Nem et al., 2003) , antibacterial (Prasad et al., 2005), (Kidwai et al., 2007), antifungal (Knoiecznyet al., 2007), anticonvulsant (Ozdemir et al., 2007), anti-inflammatory (Hsin-kaw et al., 1998), (Udupi .et al., 1998), anti-tumor agents(Kumar et al., 2003), antioxidant (Anto et al., 1995),(Vaya et al., 1997), (Mukherjee et al., 2001), antidiabetic, anesthetic and analgesic (Regaila et al., 1979),(Krishna,1980).

Material and Methods

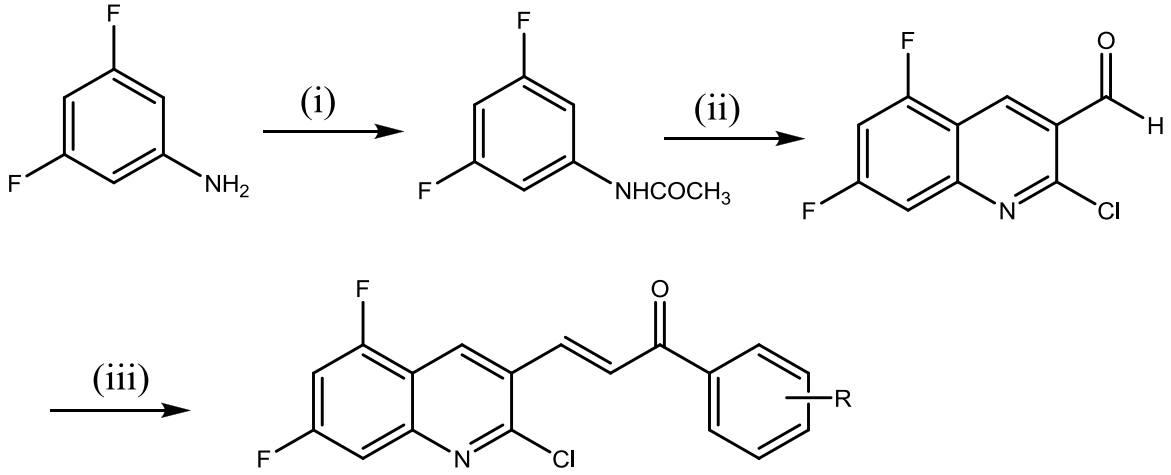
All the melting points were measured in open capillary tube in scientific melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed on silica gel plate(Merck, 60, F254) was used for purity checking and reaction monitoring. IR Spectra of synthesized compound were scanned on Shimnshu – FTIR. ^{1}H NMR spectra were measuredin $CDCl_3$ or DMSO on a BRUKER AVANCE II 400 spectrometer and tetramethylsilane (TMS) as an internal standard.All reagents used in the present work were of analytical grade.

General procedure for the 2-choro-3-formyl quinoline.

To a solution of acetanilide (0.05mol) in dry DMF (0.15 mol) at 0-5 ^{0}C temperature, phosphoryl chloride (0.35mol) was added drop wise with stirring and mixture was reflux at 85-90 ^{0} C for time ranging between 4-16 hours. The mixture was poured into crushed ice, stirred for 1h and kept overnight. The resulting solid was filtered, washed well with water and dried. The compound was recrystallised from ethyl acetate .

General procedure for the synthesis of chalcone

Equimolar quantities of 2-chloro-5,7-diflouroquinoline-3-carbaldehyde(0.001mol) and substituted acetophenone (0.001 mol) in methanol wasstirredat 0-5^0 C for 2h, while drop wise additionof aqueous sodium hydroxide (NaOH 25%, 4.0ml)to the solution and stirring was continuous for 24 h at room temperature. The reaction mixture was poured into crushed ice and acidified if necessary with dilute hydrochloric acid (10% HCl). The solid mass separated out was filtered, washed with water and crystallized from ethanol to yellow product.The residue was purified by column chromatography using ethanol.



R= 4-Chloro, 4-Bromo, 4-methoxy, 4-Amino, 3-Flour, 3-Methoxy, 2,4-Di flour, 2,4-dichloro 5-flouro, 2,4-diflouro 5-chloro, 2,4,5- trichloro.

Scheme 1 (i)Acetic acid, acetic anhydride, reflux for 3-4 hours. (ii) DMF+$POCl_3$ reflux at 80^0 C for 4-16 hour. (iii) substituted acetophenone, 25% aqueous NaOH 4 m.l and stirred for 24 h.

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(4-chlorophenyl)prop-2-en-1-one[VA-1] : M.F.: $C_{18}H_9Cl_2F_2NO$, Yield%: 70.91%, m.p.: 153-155^{0}C, IR (KBr cm^{-1}):1681.81(C=O), 1639.38(CH=CH), 3085.89(aromatic CH), 1581.52(aromatic C=N).,^{1}H NMR (DMSOppm):7.73(1H, d, Hα), 8.13 (1H, d, Hβ),7.52 (2H, d, H3'5'),7.83 (2H, d, 2'6'),8.67 (1H, s, H4), 6.52 (1H, s, H6),7.12 (1H, s, H8).

(E)-1-(4-Bromophenyl)-3-(2-chloro-5,7-diflouroquinoline-3-yl)prop-2-en-1-ene[VA-2]: M.F.: $C_{18}H_9BrClF_2NO$, Yield: 81.52%, m.p.: 165-166^{0}C, IR (KBr cm^{-1}): 1690.00(C=O), 1643.24(CH=CH), 2998.00(aromatic CH), 1585.38(aromatic C=N)., ^{1}H NMR (DMSOppm):7.59 (1H, d, Hα), 8.03 (1H, d, Hβ),7.61 (2H, d, H3'5'),7.92 (2H,d, 2'6'),8.58 (1H, s, H4), 6.59 (1H, s, H6), 7.09 (1H, s, H8).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one[VA-3]:M.F.: $C_{19}H_{12}ClF_2NO_2$, Yield: 74.24**%**, m.p.: 196-198 ^{0}C, IR (KBr cm^{-1}): 1693.38(C=O), 1639.38(CH=CH), 3062.12(aromatic CH), 1577.66(aromatic C=N)., ^{1}H NMR (DMSOppm):7.40 (1H, d, Hα), 8.11 (1H, d, Hβ),7.32 (2H, d, H3'5'),7.89 (2H, d, 2'6'), 3.67 (3H, s, H4'), 8.70 (1H, s, H4), 6.71 (1H, s, H6),7.49 (1H, s, H8).

(E)-1-(4-Aminophenyl)-3-(2-chloro-5,7-diflouroquinoline-3-yl)prop-2-en-1-ene[VA-4]: M.F.: $C_{18}H_{11}ClF_2N_2O$, Yield: 60.61**%**, m.p.: 221-223^{0}C,IR(KBrcm^1): 1676.03 (C=O), 1622.02 (CH=CH), 3068.53 (aromatic CH), 1596.95 (aromatic C=N)., ^{1}H NMR (DMSOppm):] 7.70 (1H, d, Hα), 8.00 (1H, d, Hβ),6.32 (2H, d, H3'5'),7.52 (2H, d, 2'6'), 6.14 (2H, s, H4'), 8.54 (1H, s, H4), 6.70 (1H, s, H6),7.42 (1H, s, H8).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(3-flourophenyl)prop-2-en-1-one[VA-5]: M.F.: $C_{18}H_9ClF_3NO$, Yield: 77.27**%**, m.p.: 117-118 ^{0}C, IR (KBr cm^{-1}): 1686.00 (C=O), 1634.00 (CH=CH), 3052.00 (aromatic CH), 1587.28 (aromatic C=N).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(3-methoxyphenyl)prop-2-en-1-one[VA-6]: M.F.: $C_{18}H_{12}ClF_2NO_2$, Yield: 64.85**%**, m.p: 131-132 ^{0}C, IR (KBr cm^{-1}): 1668.31 (C=O), 163938 (CH=CH), 3064.68 (aromatic CH), 1581.52 (aromatic C=N).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(2,4-diflourophenyl)prop-2-en-1-one[VA-7]: M.F.: $C_{18}H_8ClF_4NO$, Yield: 79.24**%**, m.p.: 112-114 ^{0}C, IR (KBr cm^{-1}): 1681.81(C=O), 1610.45 (CH=CH), 3070.76 (aromatic CH), 1595.02 (aromatic C=N)., ^{1}H NMR (DMSOppm):7.67 (1H, d, Hα), 8.01 (1H, d, Hβ),7.28 (1H, d, H5'),7.78 (1H, d, 6'), 6.73 (1H, s, H3'), 8.53 (1H, s, H4), 6.61 (1H, s, H6),7.35 (1H, s, H8).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(2,4-dichloro-5-flourophenyl)prop-2-en-1-one[VA-8]: M.F.: $C_{18}H_7Cl_3F_3NO$, Yield: 92.42**%**, m.p.: 212-214 ^{0}C, IR (KBr cm^{-1}): 1685.38 (C=O), 1628.68 (CH=CH), 3013.91 (aromatic CH), 1593.62 (aromatic C=N).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(2,4-diflouro-5-chlorophenyl)prop-2-en-1-one[VA-9]: M.F.: $C_{18}H_7Cl_2F_4NO$, Yield: 78.79**%**, m.p.: 198-200 ^{0}C, IR (KBr cm^{-1}): 1677.95 (C=O), 1641.31 (CH=CH), 3072.18 (aromatic CH), 1585.38 (aromatic C=N).

(E)-3-(2-Chloro-5,7-diflouroquinoline-3-yl)-1-(2,4,5-trichlorophenyl)prop-2-en-1-one[VA-10]: M.F.: $C_{18}H_7Cl_4F_2NO$, Yield: 83.33**%**, m.p.: 202-203 ^{0}C, IR (KBr cm^{-1}): 1689.34 (C=O), 1637.10 (CH=CH), 3013.91 (aromatic CH), 1580.81 (aromatic C=N).

Antimicrobial Activity

The in vitro antimicrobial activity was done by the reported method (Bauer et al., 1966). All the title compounds were screened for antibacterial activity against Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Bacillussubtilis and antifungal activity against Candida albicans, Saccheromycescervecieaceae using Ciprofloxacin, Penicillin, Cefotaxime (50 μg/ml) as standard. At the end of 18-20 hours for bacteria and fungi, the inhibition was recorded measuring the diameter of inhibition zone in mm respectively. Kirby- Bauer method was employed for anti-microbial activity. The results obtained are given in Table 1 (Bauer et al., 1966).

Results and Discussion:

New class of substituted chalcones weresynthesised and characterized by IR and ^{1}H NMR. All synthesized compounds were screened for antibacterial activity against Gram-positive (Staphylococcus aureus and Bacillus subtilis) and gram negative bacteria (Escherichia coli, Proteus vulgaris). The compound were also tested against two fungal strains, Candida albicans, Saccheromycescervecieaceae by using Kirby- Bauer method. The compound VA1, VA3, VA4 and VA9 shows good antibacterial activity and VA7 and VA8 moderate to good active. Fungicidal screening data also revealed that compound VA1, VA3, VA7 and VA9 shows moderate to good activity.

Table - 1

Sample code	Zone diameter in millimeter (mm)					
	Escherichia coli	**Proteus vulgaris**	**Staphylococcus aureus**	**Bacillus subtilis**	**Candida albicans**	**Saccheromycescervecieaceae**
VA-1	S(20)	R	R	R	S(15)	R
VA-2	R	R	R	R	R	R
VA-3	R	S(18)	S(20)	R	S(17)	S(16)
VA-4	S(20)	R	R	S(20)	R	R
VA-5	R	R	R	R	R	R
VA-6	R	R	R	R	R	R
VA-7	S(18)	R	R	S(17)	S(16)	R
VA-8	R	R	S(18)	R	R	R
VA-9	R	R	S(19)	R	R	S(15)
VA-10	R	R	R	R	R	R

R = RESISTANT (No zone of inhibition seen)

S = SENSITIVE (Zone of inhibition seen)

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