



Synthesis and study of antimicrobial agent 3-(3-substituted-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid

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Abstract

Present work describes the Synthesis of 3-(3-substituted-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid derivatives by Pfitzinger reaction of isatin with 2(1H-indol-1-yl)-1-phenyl ethanone and 1-phenyl-2-[-3-(substituted)-1-H-indole-1-yl] ethanone. The structures of all the compounds are established by elemental analysis, IR, ¹H NMR and Mass spectral data. These compounds possess excellent antimicrobial activity against bacteria and fungi.

Keywords: Chalcone, Schiff's base Chalcone, Quinazoline derivatives, antimicrobial activities.

INTRODUCTION

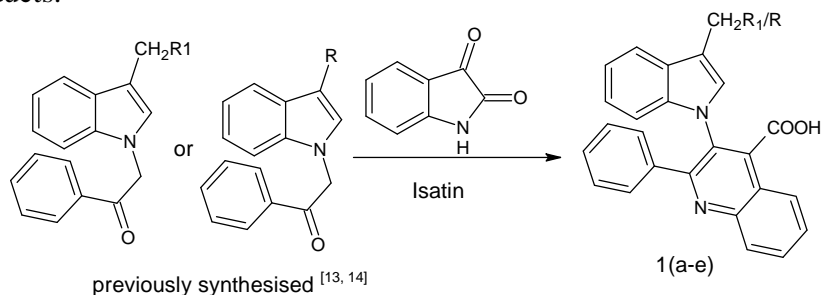
The quinoline nucleus is an important structural moiety in a number of complex chemotherapeutic agents. Substituted quinoline and their benzo and hetero fused analogues represent an important class of heterocyclic compounds because of their presences in numerous biologically active natural products. Quinoline -4-carboxylic acid and their analogues have a wide variety of medicinal properties including antitumour, antiviral and antibacterial activities [1, 2]. The Pfitzinger reactions offer a very convenient synthetic entry to quinoline 4-carboxylic acids derivative from isatin using Pfitzinger reaction. The enolizable conjugated ketone compounds condensed with isatin in strongly alkaline medium and subsequently cyclizes to give the quinoline products. This reaction provides a very facile one pot synthetic route to quinoline-4-carboxylic acid derivatives from conjugated ketone.

Exploitation of isatin moiety in antiviral and anticonvulsant area has been especially fruitful [3]. Recently, derivatives of quinoline carboxylic acid have been studied as potential HIV-I inhibitors [4]. It has stimulated a renewed interest in these molecules from yet another perspective.

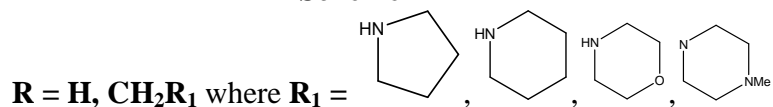
The structural core of quinoline has generally been synthesized by various conventional named reactions such as Skraup [5], Doebner-von Miller [6], Friedlander [7], Pfitzinger [8], Conrad-Limpach [9], Combes [10]. These classical syntheses are well known and still used frequently for the preparation of quinoline backbone. However, these methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system [11].

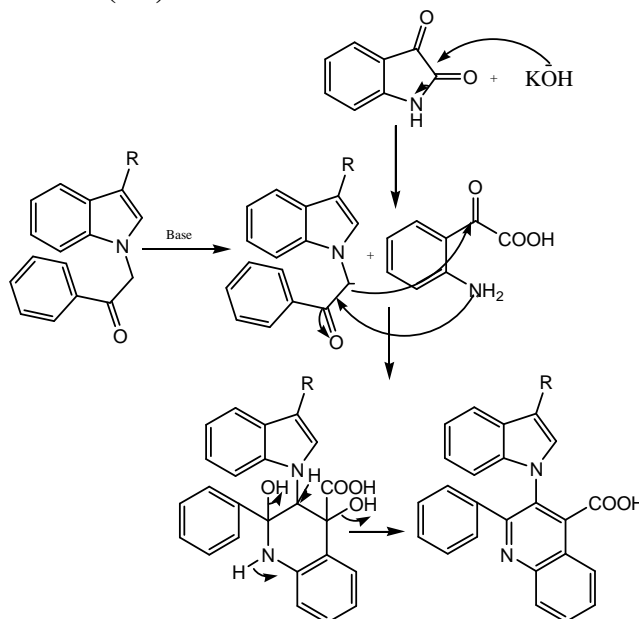
Among the synthetic strategy which could be conceived for the synthesis of quinoline derivatives, the Pfitzinger reaction offers a very convenient synthetic entry to the quinoline 4-carboxylic acid derivatives from isatin and an appropriate ketone compounds. It's wide spread application in the synthesis of quinoline and condensed quinoline derivatives have also been reviewed recently [12].

The aim of the present work was to study the application of Pfitzinger reaction of isatin and carbonyl compounds in the synthesis of diverse variety of condensed nitrogen heterocycles. The synthetic versatility of isatin has led to the extensive use of this compound in the synthesis. The chemoselectivity of these reactions depend on the nature of the nucleophile, substituents attached to the isatin nucleus (especially of those bonded to nitrogen atom) as well as upon the solvent and temperature employed. The initial products obtained can under go further reaction to give cyclisation products.



Scheme 1



Mechanism of formation of 1(a-e)**MATERIALS AND METHODS****3-(3-pyrrolidinyl-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (1a)**

A mixture of isatin (0.147g, 1mmol) and 1-phenyl-2-[3-(pyrrolidinyl)-1-H-indole-1-yl] ethanone (Previously synthesized [13, 14] (0.318g, 1mmol) in 50% aqueous EtOH (0.40ml) containing KOH (0.4g) was heated under reflux for 24 hours and then diluted with 50% aqueous EtOH to obtain a homogenous mixture. This was filtered and acidified with AcOH and the precipitate was collected, washed with 30% aqueous EtOH and recrystallized from MeOH to give (**1a**) (Yield = 66.23, M.P. = 208-210)

Similarly **compound 1b**, 3-(3-piperinyl-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid was synthesized. (Yield = 71.42, M.P. = 136-38)

Similarly **compound 1c**, 3-(3-morphonyl-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid was synthesized. (Yield = 70.67, M.P. = 76-78)

Similarly **compound 1d**, 3-(3-N-methyl piperazine-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid was synthesized. (Yield = 72.99, M.P. = 118-20)

3-(1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (9.1e)

A mixture of isatin (0.147g, 1mmol) and 1-phenyl-2-[1-H-indole-1-yl] ethanone (Previously synthesized[13,14] (0.235g, 1mmol) in 50% aqueous EtOH (0.40ml) containing KOH (0.4g) was heated under reflux for 24 hours and then diluted with 50% aqueous EtOH to obtain a homogenous mixture. This was filtered and acidified with AcOH and the precipitate was collected, washed with 30% aqueous EtOH and recrystallized from MeOH to give (**1e**) (Yield = 67.01, M.P. = 110-12)

RESULT AND DISCUSSION

IR spectra of the 3-(3-pyrrolidinyl-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (**1a**) displayed a mild peak near 1625 cm^{-1} for C=O groups. Appearance of additional peak near 3500 cm^{-1} for COOH and near 1350 cm^{-1} for C=N and disappearance of peak near 1700 cm^{-1} for C=O group suggested the formation of **compound 1a**. Similarly **compound 1(b-e)** shows the peaks.

^1H NMR (CDCl_3/TMS) spectrum of **compound 1a** displayed signals for the presence of 23 protons. A singlet at δ 11.0 which exchanged with D_2O was attributed the presences of carboxylic acid group in the molecule. The aromatic region consisted of two multiplets one containing around the region of δ 7.8-9.1 due the 4 protons of quinoline ring and a multiplet for 5 protons of indole ring. There is a singlet at δ 3.50 for 2 protons of CH_2 and one singlet for pyrrolidinyl protons at δ 1.59 and 2.25. Similarly **compound 1(b-e)** represents the NMR peaks.

Table 1: Physical and Analytical data of the compounds 1(a-e)

S. No.	Compound No.	Molecular formula	M.W.	M.P.(°C)	Yield (%)	Elemental analysis (Cal./Found) N
1.	1a	$\text{C}_{29}\text{H}_{23}\text{N}_3\text{O}_2$	448	157-60	66.23	9.39/ 9.33
2	1b	$\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_2$	462	127-30	71.42	9.10/9.23
3	1c	$\text{C}_{29}\text{H}_{25}\text{N}_3\text{O}_3$	464	88-90	70.62	9.07/9.02
4	1d	$\text{C}_{30}\text{H}_{28}\text{N}_4\text{O}_2$	477	118-20	72.99	11.76/11.70
5	1e	$\text{C}_{24}\text{H}_{16}\text{N}_2\text{O}_2$	364	90-95	67.01	7.69/7.69

Table 2: Spectral data of compounds 1(a-e)

S.No.	Comp.	IR (KBr) cm^{-1}	^1H NMR ($\text{CDCl}_3 + \text{DMSO-d}_6$) δ (ppm)	Mass (ESI) $784\mu\text{s}$ (Accumulation time) m/z
1	1a	1240(str. C-N), 1465(str. C=N), 1625(str. C=O), 3550(str. COOH)	1.59,2.25(8H,t&m,CH, pyrrol), 3.50 (2H,s, CH_2), 7.8, 8.3, 9.1(4H,d, CH, aryl), 7.13-7.99(5H,d, CH, indole) 7.16-7.99(5H, d, CH, aryl), 11(1H, s, OH)	448($\text{M}^+ + 1$)(2 4.48), 124(100%), 84(6.12%)
2	1b	1240(str. C-N), 1465(str. C=N), 1625(str. C=O), 3550(str. COOH)	1.59, 1.50, 2.25 (10H, t & m, CH, piperi.), 3.50 (2H,s, CH_2), 7.8, 8.3, 9.1(4H,d, CH, aryl), 7.13-7.99(5H,d, CH, indole) 7.16-7.99(5H, d, aryl), 11(1H, s, OH)	----
3	1c	1240(str. C-N),	1.59, 2.37, 3.62(8H, m, CH,	----

		1465(str. C=N), 1625(str. C=O), 3550(str. COOH)	morpholine), 3.50 (2H,s, CH ₂), 7.8, 8.3, 9.1(4H,d, CH, aryl), 7.13-7.99(5H,d, CH, indole) 7.16-7.99(5H, d, CH, aryl), 11(1H, s, OH)	
4	1d	1240(str. C-N), 1465(str. C=N), 1625(str. C=O), 3550(str. COOH) 1775(str. CH ₃)	1.59, 2.46(8H, m, CH, N-methyl piperazine), 3.50 (2H,s, CH ₂), 2.27(3H,s,CH ₃) 7.8, 8.3, 9.1(4H,d, CH, aryl), 7.13-7.99(5H,d, CH, indole) 7.16-7.99(5H, d, CH, aryl), 11(1H, s, OH)	----
5	1e	1240(str. C-N), 1465(str. C=N), 1625(str. C=O), 3550(str. COOH)	6.6-7.99(5H,d, CH, indole) 7.00-7.99(5H, d, CH, aryl), 7.8, 8.3, 9.1(4H,d, aryl), 11(1H, s, OH)	364,(M ⁺ +1), 319(40%), 124(100%)

Antimicrobial activity:

Antibacterial activity: Newly synthesized compounds **1(a-e)** were screened for their in-vitro antifungal activity against *Escherichia coli* and *Bacillus cereus* applying disc diffusion method. The percentage of inhibition was determined at constant concentration of test (166.66µl/disc) and standard (166.66µl/disc) by dilution using dimethylsulphoxide as a solvent. Penicillin was used as a standard in these antibacterial screening studies. The results are presented in **Table 3**.

Antifungal studies: The antifungal studies of compounds **1(a-e)** were performed by the standard agar disc diffusion method. Seven days old culture of *Fusarium oxysporium* and *Macrophomina phaeolina* were used as test organism. They were grown on Potato Dextrose Agar medium. The percentage of inhibition was determined at constant concentration of test and standard by dilution technique using dimethylsulphoxide as solvent. The growth of micro-organism was determined visually and the growth of the micro-organism for 24 hrs at 37⁰C was taken. The standard used for the comparison in antifungal screening was Fluconazole. The results are presented in **Table 4**.

The solution of standards, penicillin (antibacterial activity) and fluconazole (antifungal activity), were prepared in dimethylsulphoxide. A control experiment with dimethylsulphoxide alone was done for both the antibacterial and antifungal studies

Antibacterial and antifungal activities of all newly prepared compounds against two bacteria and two fungi are presented in **Table 3** and **Table 4**. Against *E. coli* compound 1a showed greatest activity. It was greater than standard and compound 1e had the lowest activity. When activity were done against *B. cerus* it was found that compound 1b was most potent and compound 1e showed lowest activity but all the compounds have had greater activity than the standard drug. In the same way for the study of fungus that is *F. oxysporium*, it was concluded that compound 1d was most active and compound 1a was least active. Data clearly indicates that compound 1d

was most potent and compound 1c was least active against *M. phaeolina*. Overall these compounds showed surprise results than expected

Table: 3 Antibacterial activity of compounds 1(a-e)

S. No.	Comp	Cons (µg/disc)	E .coli		B. cereus.	
			Zone of inhibition (mm) test (% activity)	Zone of inhibition (mm) (std)	Zone of inhibition (mm)(test) (% activity)	Zone of inhibition (mm) (std)
1	1a	166.66	24.00 (103.62)	23.16	28.33 (131.16)	21.50
2	1b	166.66	22.16 (83.62)	26.50	37.50 (157.36)	23.83
3	1c	166.66	19.50 (84.19)	23.16	27.33 (127.11)	21.50
4	1d	166.66	20.66 (77.96)	26.50	30.16 (126.56)	23.83
5	1e	166.66	19.50 (73..58)	26.50	27.66 (116.07)	23.83

In bracket there is percentage activity

Table: 4 Antifungal activity of compounds 1(a-e)

S. No.	Comp	Cons (µg/disc)	F. oxysporium		M. phaeolina	
			Zone of inhibition (mm)(test) (% activity)	Zone of inhibition (mm) (std)	Zone of inhibition (mm)(test) (% activity)	Zone of inhibition (mm) (std)
1	1a	166.66	19.21 (63.35)	39.35	17.21 (75.91)	22.67
2	1b	166.66	39.00 (119.37)	45.66	17.33 (75.28)	23.02
3	1c	166.66	42.32 (93.35)	35.66	12.00 (51.76)	23.18
4	1d	166.66	40.55 (124.11)	39.35	26.33 (113.58)	23.18
5	1e	166.66	31.44 (96.23)	35.66	22.33 (96.33)	23.18

In bracket there is percentage activity

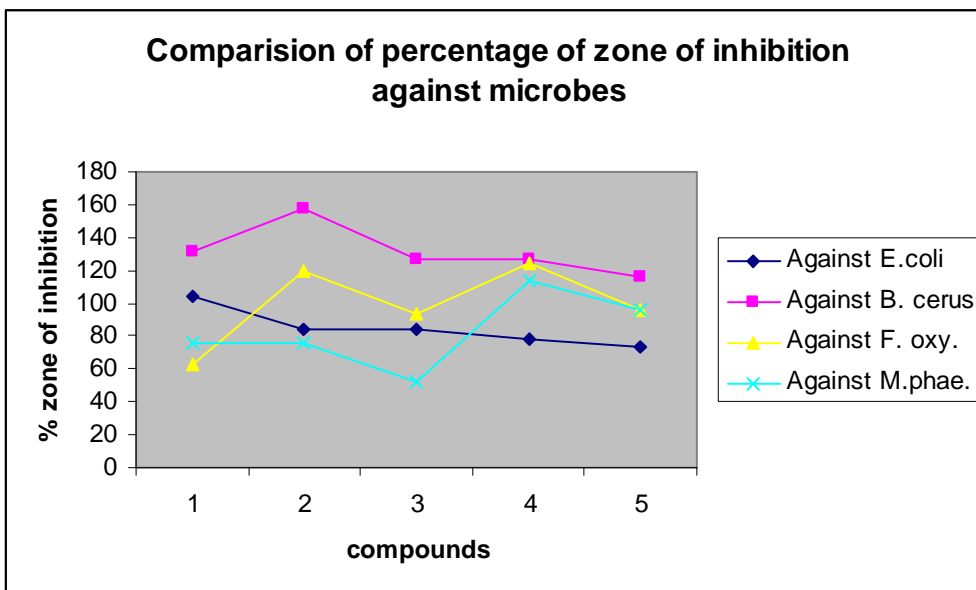
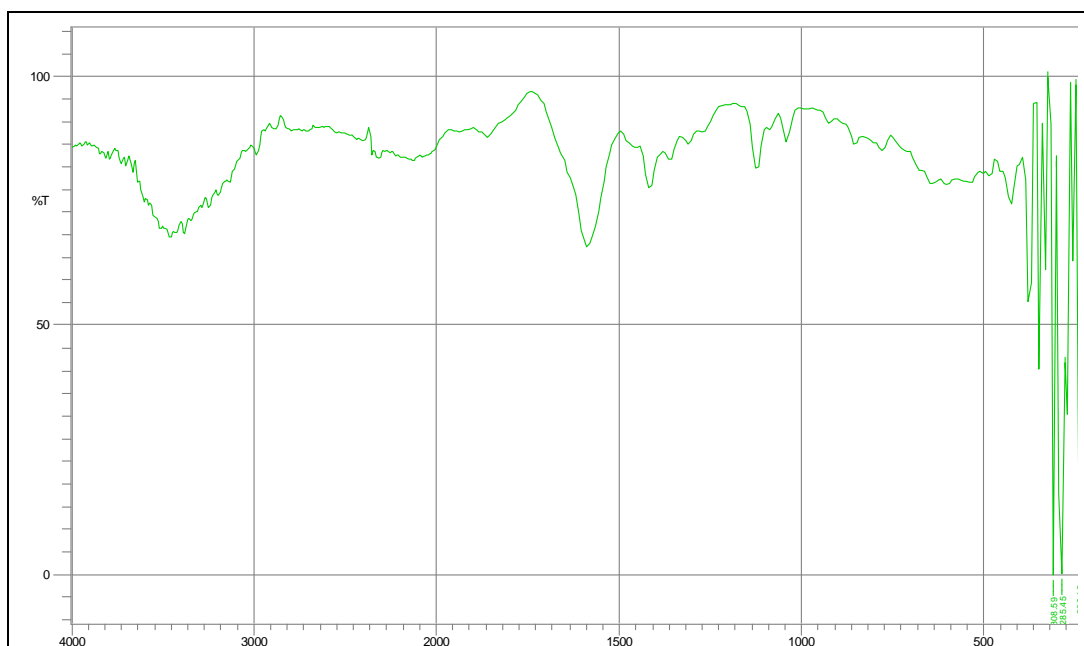
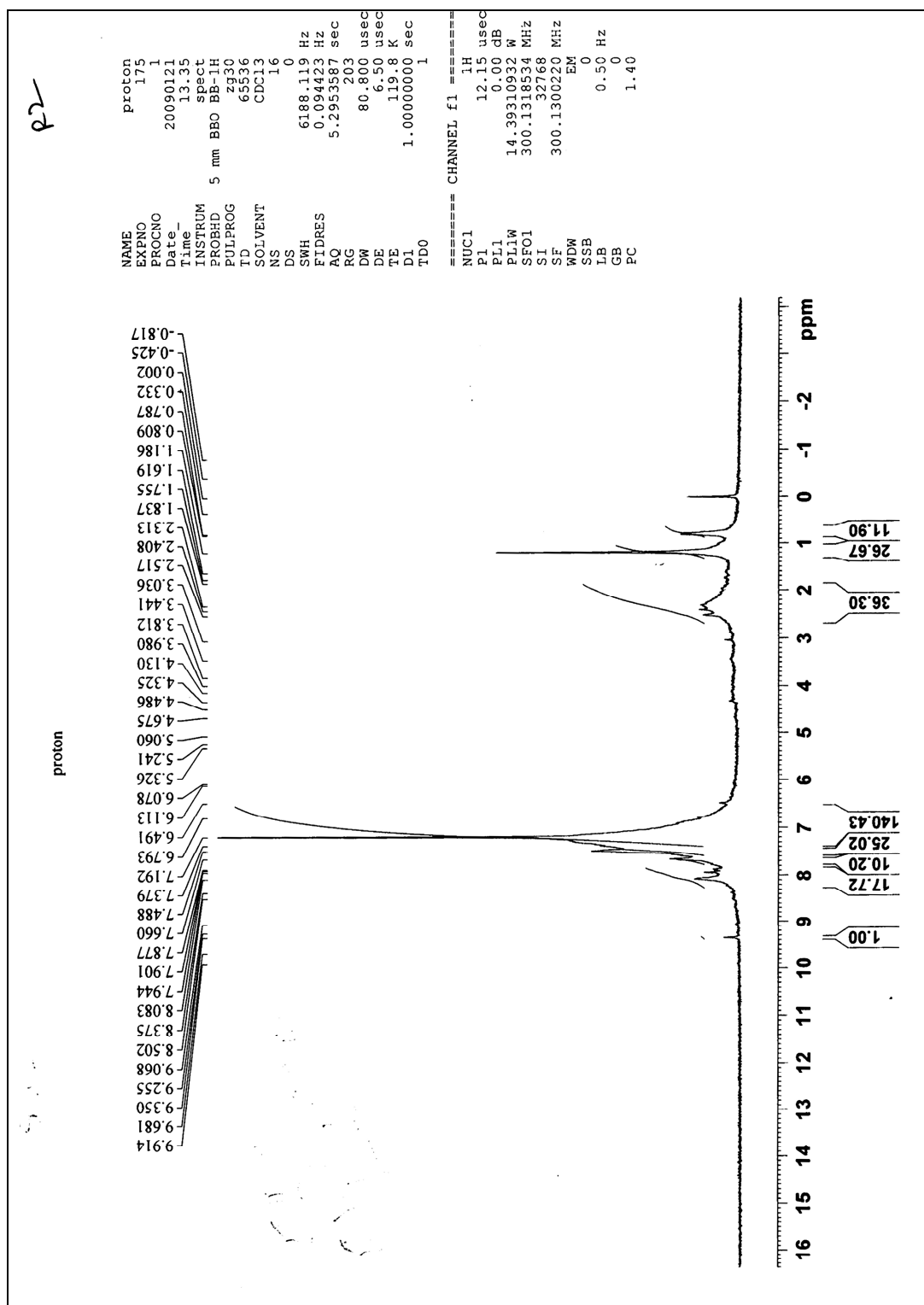


Fig:1 F.oxy = *F. oxysporium*, M. phae. = *M.pheolina*

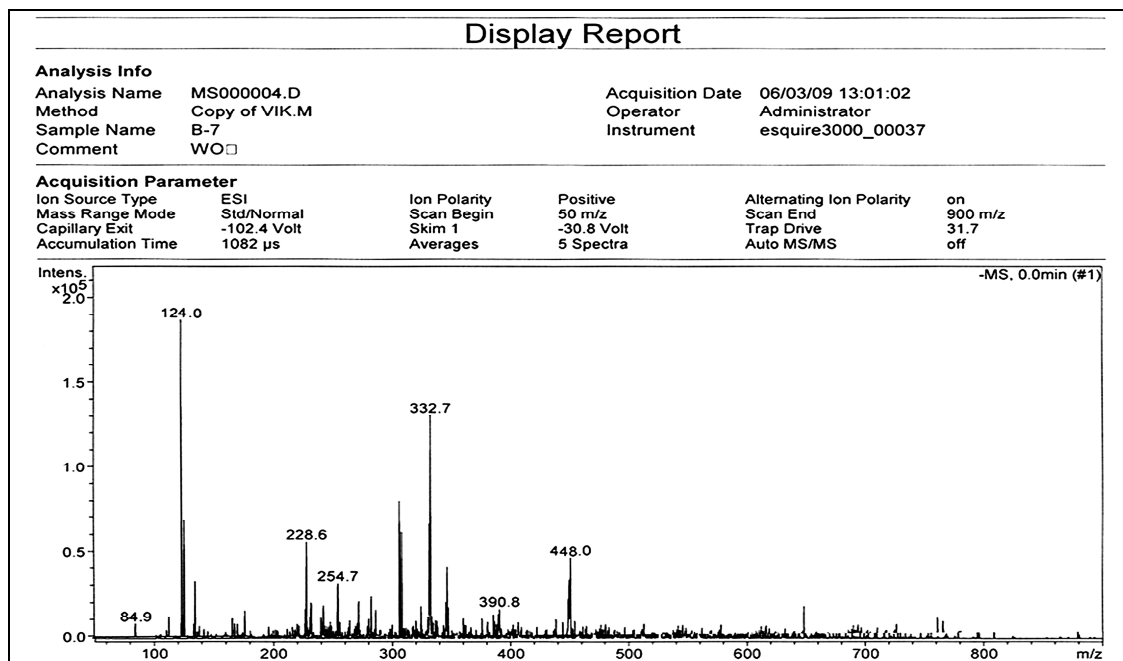
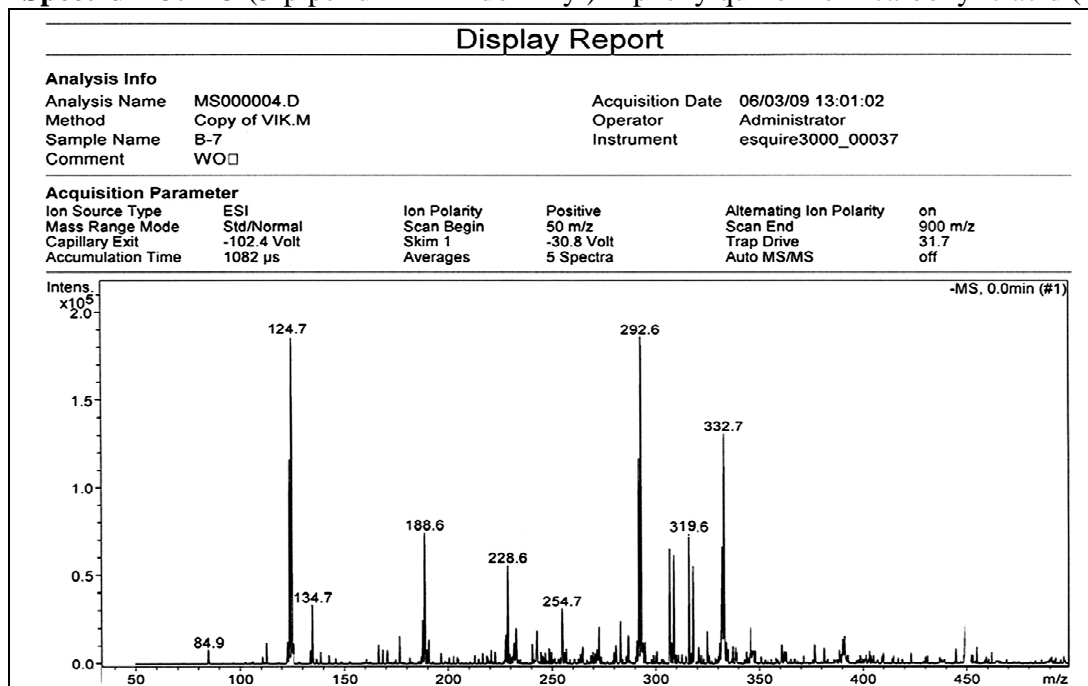
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Spectrum 1: 3-(3-N-methylpiperazine-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (1d)



Spectrum 2: 3-(1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (1e)

**Spectrum 3:** 3-(3-piperidin-1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (**1a**)**Spectrum 4:** 3-(1H-indon-1-yl)-2-phenylquinoline-4-carboxylic acid (**1e**)

CONCLUSION

In view of the impressive pharmacodynamic applications shown by conjugated ketone of indole derivatives, much attention has focused towards developing new synthetic routes to substituted and hetero ring fused with conjugated ketone moiety [13]. The synthesis of this series of heterocycle was undertaken in the present work with this assumption that the incorporation of one or more than one heterocycle moiety in conjugated ketone could result in molecules with enhanced bio-activity. This work describes the study based on this assumption and presents the synthesis of variously substituted indole derivatives from isatin using Pfitzinger reaction. In the present work, the synthesis of substituted quinoline carboxylic acids **1(a-e)** was carried out using Pfitzinger reaction on isatin and conjugated ketones.

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