Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol 6, Suppl 2, 2013 ISSN - 0974-2441

Research Article

SYNTHESIS AND PHARMACOLOGICAL STUDIES OF SOME NOVEL BENZOQUINOLINE DERIVATIVES

ALPANA J ASNANI*, SHASHIKANT SAHARE

J. L. Chaturvedi College of Pharmacy,Electronic Zone Building, M.I.D.C., Hingna road, Nagpur-440 016.,E-mail:ajasnani7@gmail.com

Received: 25 March 2013, Revised and Accepted: 11 April 2013

ABSTRACT

The present research work was aimed to synthesis some novel substituted of Benzo[*f*]quinoline compounds. The twenty five derivatives of Benzo[*f*]quinoline has been synthesized using appropriate synthetic route. The structure and purity of compounds were confirmed by means of IR, H^1NMR, mass spectral studies, elemental analysis and physicochemical analysis. All the compounds were evaluated for analgesic and anti-inflammatory activity by Hot Plate Method and Carrageenan Induced Rat Paw Edema Method respectively and they showed significant activity when given orally. The toxicity study of all synthesized compounds has been determined and LD_{50} was found to be ≥ 100mg/Kg. Compounds IV c, f, g, k and I showed good analgesic activity and Comp. IV u as well as comp. IV v was found to possess moderate analgesic activity as compared with standard drug Tramadol. All the synthesized compounds showed significant anti-inflammatory activity compared with the standard drug diclofenac sodium and comp. IV b, c, e, j, n, p and y possess good anti-inflammatory activity.

Keywords: Benzo[*f*]quinoline, analgesic activity, anti-inflammatory activity

INTRODUCTION

The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties[1].Benzoquinoline belong to the azaarenes, a family of nitrogen containing polycyclic aromatic hydrocarbons, in which one 'C' atom of the aromatic ring structure has been replaced by an 'N' atom. Four benzoquinoline isomers are commercially available: benzo[*b*]quinoline (acridine), benzo[*c*]quinoline (phenanthridine), benzo[*f*]quinoline, and benzo[*h*]quinoline[2]. The synthesis of benzo[*f*]quinoline is based on the condensation of Schiff bases derived from 2- aminonaphthalene-1-sulfonic acid with various aromatic, aliphatic and heterocyclic benzaldehydes. The formation of benzo[*f*]quinoline is a multistep process. The condensation of Schiff bases with ketones are catalyzed by acids. Proton addition to a Schiff base yields the corresponding cation in which the positive charge is delocalized over the azomethine nitrogen and carbon atoms. Therefore such cations readily take up even weakly nucleophilic ketones. The reaction mechanism is analogous to the acid catalyzed aldol addition pattern. Hence substituted benzo[*f*]quinoline was planned to synthesized and evaluate newly synthesized compounds for their analgesic and anti-inflammatory activity[3].

MATERIAL AND METHODS

All the chemicals used in the present work were AR grade and LR grade, purchased from Loba, Merck and Fisher scientific fine chemicals. The melting points were recorded by open capillary using LABHOSP melting point apparatus and were uncorrected. The purity and homogeneity of the synthesized compounds was routinely ascertained by the thin layer chromatography[4], performed on plates coated with silica gel- G using the solvent system benzene: methanol: acetone (7:2:1). The absorption maxima of the synthesized compounds were recorded in methanol (analytical grade, 1mg/100mL). The methanolic solution of the synthesized compounds were scaned on Shimadzu UV 1601 spectrophotometer, Japan; in the region 200-400nm. The IR spectra[4] were recorded in KBr disc on FTIR Shimadzu 8400. The 1H-NMR spectra[4] were recorded on Bruker Avance II 400 NMR spectrometer using DMSO as solvent and TMS as an internal solvent. The Mass spectra[4] were recorded on Waters Q –Toff-micro spectrometer. The Analgesic and Anti-inflammatory activity evaluation were carried out using hot plate method[5] on mice by using higher dose 20 mg/Kg and carrageenan- induced rat paw edema method on albino rats by using higher dose 50 mg/Kg and compared with the group receiving a standard drug Tramadol and Diclofenac sodium respectively.

EXPERIMENTAL

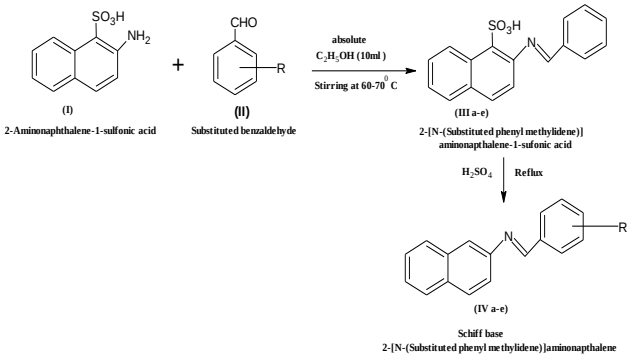
Scheme A- Synthesis of 2-[N- phenyl methylidene]amino napthalene.

A mixture of solution of 2-aminonapthalene-1-sulfonic acid (2.23g, 0.01mole) and benzaldehyde (0.01mole) in absolute ethanol (10 mL each) was stirred at 60–70°C for 2 h gives 2(N-substituted phenyl methylidene)-aminonapthalene-1-sulfonic acid Comp. III. Cool it and collect the precipitate by filtration and recrystallised from absolute ethanol. Further Comp. III was reflux in presence of H_2SO_4 for 24 h yield 2(N-phenyl methylidene) - aminonapthalene Comp. IV a. Four more derivatives were prepared using different benzaldehydes Comp. IV (b-y).

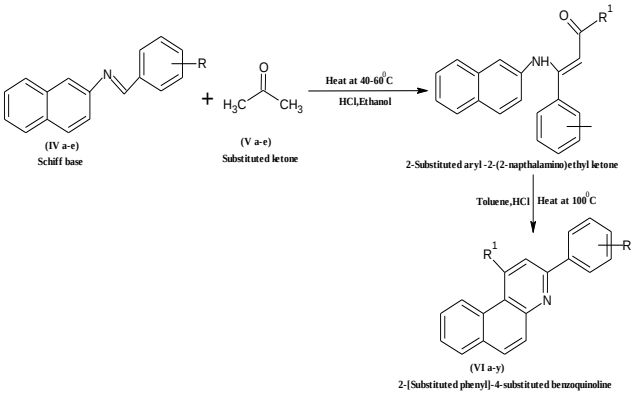
Scheme B- Synthesis of 4-methyl-2-phenyl benzo[*f*]quinoline

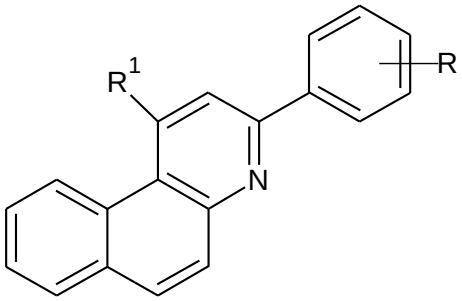
The mixture of comp. IV a (0.01 mole) and acetone (0.01 mole) were heated for 4-5 h at 40-60ºC in presence of concentrated hydrochloric acid (3-4 drops) and ethanol (10 mL) yield 2-aryl-2-(napthalamino) ethyl ketone further heating in presence of toluene (10 mL) and concentrated hydrochloric acid (3-4 drops) at 110ºC yield 4-phenyl-2-phenyl benzo[*f*]quinoline Comp. VI a. Twenty four more derivatives were prepared using same procedure and different ketones Comp. VI (b-y)

Scheme



Scheme A- Synthesis of 2-[N- phenyl methylidene]aminonapthalene.





2-[substituted phenyl]-4-substituted benzo[*f*]quinoline

Scheme B: Synthesis of 4-methyl-2-phenyl benzo[f]quinoline

General structure

TABLE 1: SYNTHESIZED DERIVATIVE OF 2-[SUBSTITUTED PHENYL]-4-SUBSTITUTED BENZO[*F*]QUINOLINE

Sr. No.	Compound Code	R	R^1
1	**VI a**	-H	$-CH_3$
2	**VI b**	-H	$-COCH_3$
3	**VI c**	-H	$4-NO_2$
4	**VI d**	-H	4-OH
5	**VI e**	-H	3-OH
6	**VI f**	$4-CH_3$	$-CH_3$
7	**VI g**	$4-CH_3$	$-COCH_3$
8	**VI h**	$4-CH_3$	$4-NO_2$
9	**VI i**	$4-CH_3$	4-OH
10	**VI j**	$4-CH_3$	3-OH
11	**VI k**	$3-NO_2$	$-CH_3$
12	**VI l**	$3-NO_2$	$-COCH_3$
13	**VI m**	$3-NO_2$	$4-NO_2$
14	**VI n**	$3-NO_2$	4-OH
15	**VI o**	$3-NO_2$	3-OH
16	**VI p**	$4-N(CH_3)_2$	$-CH_3$
17	**VI q**	$4-N(CH_3)_2$	$-COCH_3$
18	**VI r**	$4-N(CH_3)_2$	$4-NO_2$
19	**VI s**	$4-N(CH_3)_2$	4-OH
20	**VI t**	$4-N(CH_3)_2$	3-OH
21	**VI u**	4-OH	$-CH_3$
22	**VI v**	4-OH	$-COCH_3$
23	**VI w**	4-OH	$4-NO_2$
24	**VI x**	4-OH	4-OH
25	**VI y**	4-OH	3-OH

TABLE 2:PHYSICOCHEMICAL PROPERTIES OF SYNTHESIZED COMPOUNDS

Comp. No.	Comp. Name	Molecular formula	Molecular weight	m.p (^{0}C)	% yield	R_f value
VI a	4-Methyl-2-phenyl benzo[*f*]quinoline	$C_{20}H_{15}N$	269	166-168	67	0.42
VI b	2,4-Diphenyl benzo[*f*]quinoline	$C_{25}H_{15}N$	331	228-230	59	0.55
VI c	4-(4-Nitro phenyl)-2-phenyl benzo[*f*]quinoline	$C_{25}H_{16}N_2O_2$	376	272-274	60	0.24
VI d	4-(4-Hydroxyphenyl)-2-phenyl benzo[*f*]quinoline	$C_{25}H_{17}NO$	347	244-246	58	0.16
VI e	4-(3-Hydroxy phenyl)-2-phenyl benzo[*f*]quinoline	$C_{25}H_{17}NO$	347	245-247	49	0.11
VI f	2-(4-Methoxy phenyl)-4-methyl benzo[*f*]quinoline	$C_{21}H_{17}NO$	299	196-198	43	0.32
VI g	2-(4-Methoxy phenyl)-4 –phenyl benzo[*f*]quinoline	$C_{26}H_{19}NO$	361	258-260	72	0.25
VI h	2-(4-Methoxy phenyl)-4-(4-nitro phenyl) benzo[*f*]quinoline	$C_{25}H_{18}N_2O_3$	406	278-280	65	0.23
VI i	2-(4-Methoxy phenyl)-4-(4-hydroxy phenyl) benzo[*f*]quinoline	$C_{26}H_{19}NO_2$	377	274-276	67	0.42
VI j	2-(4-Methoxy phenyl)-4-(3-hydroxy phenyl) benzo[*f*]quinoline	$C_{26}H_{19}NO_2$	377	276-278	63	0.15
VI k	2-(3-Nitro phenyl) -4 -methyl benzo[*f*]quinoline	$C_{20}H_{14}N_2O_2$	314	211-213	60	0.11
VI l	2-(3-Nitro phenyl)-4-phenyl benzo[*f*]quinoline	$C_{25}H_{16}N_2O_2$	376	275-277	49	0.42
VI m	2-(3-Nitrophenyl)-4-(4-nitrophenyl)	$C_{25}H_{15}N_3O_4$	421	279-281	61	0.35

	benzo[*f*]quinoline					
VI n	2-(3-Nitrophenyl)-4-(4-hydroxy phenyl) benzo[*f*]quinoline	$C_{25}H_{16}N_2O_3$	392	289-291	72	0.36
VI o	2-(3-Nitrophenyl)-4-(3-hydroxy phenyl) benzo[*f*]quinoline	$C_{25}H_{16}N_2O_3$	392	288-290	68	0.13
VI p	2-(4-Dimethylamino)-4-methyl benzo[*f*]quinoline	$C_{22}H_{20}N$	312	209-211	64	0.15
VI q	2-(4-Dimethylamino)-4-phenyl benzo[*f*]quinoline	$C_{27}H_{22}N$	374	271-273	54	0.14
VI r	2-(4-Dimethylamino)-4-nitro phenyl benzo[*f*]quinoline	$C_{27}H_{21}N_3O_2$	419	278-280	49	0.22
VI s	2-(4-Dimethylamino)-4-hydroxy phenyl benzo[*f*]quinoline	$C_{27}H_{22}N_2O$	390	269-271	46	0.42
VI t	2-(4-Dimethylamino)-3-hydroxyphenyl benzo[*f*]quinoline	$C_{27}H_{22}N_2O$	390	270-272	60	0.15
VI u	2-(4-Hydroxyphenyl)4-methyl benzo[*f*]quinoline	$C_{20}H_{15}NO$	285	182-184	63	0.13
VI v	2-(4-Hydroxyphenyl)4-phenyl benzo[*f*]quinoline	$C_{25}H_{17}NO$	347	244-246	64	0.44
VI w	2-(4-Hydroxyphenyl) -4-nitro phenyl benzo[*f*]quinoline	$C_{25}H_{16}N_2O_3$	392	289-291	59	0.35
VI x	2-(4 -Hydroxyphenyl)-4-hydroxy phenyl benzo[*f*]quinoline	$C_{25}H_{17}NO_2$	363	260-262	61	0.22
VI y	2-(4-Hydroxyphenyl)-3-hydroxy phenyl benzo [*f*]quinoline	$C_{25}H_{17}NO_2$	363	261-263	63	0.10

VI a: IR (KBr, V max, cm^{-1}): 2998.03 (-CH stretching), 1680.07 (Ar C=C stretching), 1339.05 (C-N stretching), 1298.93 (C-C stretching), **[1] H-NMR** (DMSO, δ ppm): 5.65 [s, 1H, CH], 7.1-7.6 [m, 5H, Ar-ring], **MS**: m/z 271 (M^+), Anal Calcd for $C_{20}H_{15}N$: C, 88.52; H, 6.31;N, 5.16. Found C, 88.42; H, 6.22; N, 5.36 %

VI b: IR (KBr, V max, cm^{-1}): 2995.12 (-CH stretching), 1672.17 (Ar C=C stretching), 1340.15 (C-N stretching), 1291.83 (C-C stretching, **[1] H-NMR** (DMSO, δ ppm): 5.41 [s, 1H, CH], 7.2-7.5 [m, 5H, Ar-ring], **MS**: m/z 333 (M^+), Anal Calcd for $C_{25}H_{15}N$: C, 84.25; H, 5.72;N, 4.68; O, 5.34. Found C, 84.31; H, 5.75; N, 4.66; O, 5.38 %

VI c: IR (KBr, V max, cm^{-1}): 1542.30 (-NO_2 stretching), 2989.16 (-CH stretching), 1675.27 (Ar C=C stretching), 1347.25 (C-N stretching), 1295.23 (C-C stretching), 1080.10, **[1] H-NMR** (DMSO, δ ppm): 5.53 [s, 1H, CH], 7.2-7.5 [m, 5H, Ar-ring], **MS**: m/z 379 (M^+) , Anal Calcd for $C_{25}H_{16}N_2O_2$:C, 75.89; H, 4.67; N, 9.27; O,10.58. Found C, 75.45; H, 4.63; N, 9.36; O,10.56 %

VI d: IR (KBr, V max, cm^{-1}): 3470.36 (-OH stretching), 2997.66 (-CH stretching), 1679.77 (Ar C=C stretching), 1350.15 (C-N stretching), 1289.23 (C-C stretching), 1087,**[1] H-NMR** (DMSO, δ ppm): 5.63 [s, 1H, CH], 7.2-7.4 [m, 5H, Ar-ring], 8.7 [s, -OH], **MS**: m/z 351(M^+), Anal Calcd for $C_{25}H_{17}NO$:C, 83.49; H, 5.53; N,5.12;O,5.85. Found C, 83.51; H, 5.55; N, 5.16; O,5.78 %

VI e: IR (KBr, V max, cm^{-1}): 3465.36 (-OH stretching), 2987.46 (-CH stretching), 1676.87 (Ar C=C stretching), 1348.55 (C-N stretching), 1290.53 (C-C stretching),**[1]H-NMR** (DMSO, δ ppm): 5.60 [s, 1H, CH], 7.1-7.3 [m, 5H, Ar-ring], 8.7 [s, -OH] , **MS**: m/z 352 (M^+), Anal Calcd for $C_{25}H_{17}NO$:C, 83.49; H, 5.53; N,5.12;O,5.85. Found C, 83.51; H, 5.55; N, 5.16; O, 5.78 %

VI f: IR (KBr, V max, cm^{-1}): 2937 (-CH_3 stretching), 1681.07 (Ar C=C stretching), 1342.05 (C-N stretching), 1288.93 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 2.05 [s, 3H, CH_3], 7.4-7.6 [m, 5H, Ar-ring], **MS**: m/z 301(M^+), Anal Calcd for $C_{21}H_{17}NO$: C, 88.39; H, 6.71; N, 4.91. Found C, 88.49; H, 6.66; N, 4.85 %

VI g: IR (KBr, V max, cm^{-1}): 2935 (-CH_3 stretching), 1678.07 (Ar C=C stretching), 1338.05 (C-N stretching), 1282.93 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 2.25 [s, 3H, CH_3], 7.4-7.8 [m, 5H, Ar-ring], **MS**: m/z 401 (M^+), Anal Calcd for $C_{26}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47; O, 5.11. Found C, 84.32; H, 6.13; N, 4.42; O, 5.13 %

VI h: IR (KBr, V max, cm^{-1}): 1538.33 (-NO_2 stretching), 2947 (-CH_3 stretching), 1680.18 (Ar C=C stretching), 1346.22 (C-N stretching), 1272.79 (C-C stretching), 1096 (C-O stretching), **[1]H-NMR** (DMSO, δ ppm): 2.15 [s, 3H, CH_3], 7.4-7.5 [m, 5H, Ar-ring], 8.1 [s, NO_2], **MS**: m/z 409 (M^+), Anal Calcd for $C_{25}H_{18}N_2O_3$: C, 75.93; H, 5.10; N, 8.85; O, 10.12. Found C, 75.85; H, 5.12; N, 8.82; O, 10.21 %

VI i: IR (KBr, V max, cm^{-1}): 3469.27 (-OH stretching), 2955 (-CH_3 stretching), 1672.48 (Ar C=C stretching), 1337.45 (C-N stretching), 1270.63 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 2.18 [s, 3H, CH_3], 7.1-7.3 [m, 5H, Ar-ring], 8.6 [s, -OH], **MS**: m/z 379 (M^+), Anal Calcd for $C_{26}H_{19}NO_2$: C, 88.59; H, 5.96; N, 4.87; O, 5.57. Found C, 88.56; H, 5.97; N, 4.82; O, 4.92 %

VI j: IR (KBr, V max, cm^{-1}): 3469.27 (-OH stretching), 2960 (-CH_3 stretching), 1660.87 (Ar C=C stretching), 1353.94 (C-N stretching), 1268.93 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 2.1 [s, 3H, CH_3], 7.1-7.4 [m, 5H, Ar-ring], 8.5 [s, -OH], **MS**: m/z 380 (M^+), Anal Calcd for $C_{26}H_{19}NO_2$: C, 88.59; H, 5.96; N, 4.87; O, 5.57. Found C, 88.56; H, 5.97; N, 4.82; O, 4.92 %

VI k: IR (KBr, V max, cm^{-1}): 2966.33 (-CH_3 stretching), 1538.33 (-NO_2 stretching), 1668.23 (Ar C=C stretching), 1348.94 (C-N stretching), 1250.07 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 7.0-7.2 [m, 5H, Ar-ring], 8.09 [s, NO_2], **MS**: m/z 317 (M^+), Anal Calcd for $C_{20}H_{14}N_2O_2$: C, 76.17; H, 4.79; N, 8.88; O, 10.15. Found C, 76.20; H, 4.76; N, 8.86; O, 10.17 %

VI l: IR (KBr, V max, cm^{-1}): 1537.13 (-NO_2 stretching), 2956.13 (-CH_3 stretching), 1651.13 (Ar C=C stretching), 1340.34 (C-N stretching), 1245.77 (C-C stretching), 1095.78 (C-O stretching), **[1]H-NMR** (DMSO, δ ppm): 7.1-7.3 [m, 5H, Ar-ring], 8.1 [s, -NO_2], **MS**: m/z 378 (M^+), Anal Calcd for $C_{25}H_{16}N_2O_2$: C, 73.46; H, 4.40; N,8.16; O, 13.98. Found C, 73.48; H, 4.42; N,8.14; O, 13.96 %

VI m: IR (KBr, V max, cm^{-1}): 1530.00 (-NO_2 stretching), 1662.13 (Ar C=C stretching), 1345.34 (C-N stretching), 1248.77 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 6.9-7.1 [m, 5H, Ar-ring], 8.12 [s, -ON_2], **MS**: m/z 424 (M^+), Anal Calcd for $C_{25}H_{15}N_3O_4$: C, 65.89; H, 3.93; N, 12.13: O, 18.48. Found C, 65.85; H, 3.92; N, 12.16: O, 18.50 %

VI n: IR (KBr, V max, cm^{-1}): 3465.27 (-OH stretching), 1535.00 (-NO_2 stretching), 1674.03 (Ar C=C stretching), 1335.12 (C-N stretching), 1240.52 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 7.2-7.3 [m, 5H, Ar-ring], 8.16 [s, -ON_2], 8.7 [s, -OH], **MS**: m/z 398 (M^+), Anal Calcd for $C_{25}H_{16}N_2O_3$: C, 71.92; H, 4.13; N, 8.83; O, 15.13. Found C, 71.90; H, 4.10; N, 8.85; O, 15.15 %

VI o: IR (KBr, V max, cm^{-1}):): 3463.27 (-OH stretching), 1533.00 (-NO_2 stretching), 1660.53 (Ar C=C stretching), 1340.64 (C-N stretching), 1235.57 (C-C stretching), 1085**[1]H-NMR** (DMSO-*d*6, δ ppm): 7.0-7.2 [m, 5H, Ar-ring], 8.1 [s, -ON_2], 8.09 [s, -OH], **MS**: m/z 395 (M^+), Anal Calcd for $C_{25}H_{16}N_2O_3$: C, 71.92; H, 4.13; N, 8.83; O, 15.13. Found C, 71.90; H, 4.10; N, 8.85; O, 15.15 %

VI p: IR (KBr, V max, cm^{-1}): 2940.12 (-CH_3 stretching), 1500.53 (Ar C=C stretching), 1300.68 (C-N stretching), 1250.02 (C-C stretching), **[1]H-NMR** (DMSO, δ ppm): 2.1 [t, 3H,-CH_3], 7.3-7.5 [m, 5H, Ar-ring], **MS**: m/z 317 (M^+), Anal Calcd for $C_{22}H_{20}N_3$: C, 89.19; H, 5.16; N, 5.20. Found C, 89.25; H, 5.18; N, 5.12 %

VI q: IR (KBr, V max, cm^{-1}): 2971.03 (-CH_3 stretching), 1662.06 (Ar C=C stretching), 1385.00 (C-N stretching), 1248.99 (C-C stretching), 1100.10 (C-O stretching), **[1]H-NMR** (DMSO, δ ppm): 2.1 [t, 3H,-CH_3], 7.2-7.9 [m, 5H, Ar-ring], **MS**: m/z 376 (M^+), Anal Calcd for $C_{27}H_{22}$ N: C,

84.82; H, 5.08; N, 4.71; O, 5.38. Found C, 84.85; H, 5.10; N, 4.70; O, 5.42 %

VI r: IR (KBr, V max, cm^{-1}): 1535.00 (-NO_2 stretching), 2980.13 (-CH_3 stretching), 1671.06 (Ar C=C stretching), 1381.02 (C-N stretching), 1258.89 (C-C stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.12 [t, 3H,-CH_3], 7.2-7.3 [m, 5H, Ar-ring], 8.5 [s, -ON_2], **MS**: m/z 422 (M^+), Anal Calcd for $C_{27}H_{21}N_3O_2$: C, 75.99; H, 4.02; N, 9.33; O, 10.66. Found C, 75.96; H, 4.01; N, 9.34; O, 10.69 %

VI s: IR (KBr, V max, cm^{-1}): 3465.00 (-OH stretching), 2982.13 (-CH_3 stretching), 1680.76 (Ar C=C stretching), 1371.82 (C-N stretching), 1268.89 (C-C stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.15 [t, 3H,-CH_3], 7.7-7.9 [m, 5H, Ar-ring], 8.1 [s, -OH], **MS**: m/z 393 (M^+), Anal Calcd for $C_{27}H_{22}N_2O$: C, 84.11; H, 4.83; N, 5.16; O, 5.90. Found C, 84.04; H, 4.75; N, 5.10; O, 5.83 %

VI t: IR (KBr, V max, cm^{-1}): 3469.30 (-OH stretching), 2970.33 (-CH_3 stretching), 1661.96 (Ar C=C stretching), 1390.62 (C-N stretching), 1250.89 (C-C stretching), **^{1}H-NMR** (DMSO-*d*6, δ ppm): 2.5 [t, 3H,-CH_3], 7.2-7.9 [m, 5H, Ar-ring], 8.09 [s, -OH], **MS**: m/z 395 (M^+), Anal Calcd for $C_{27}H_{22}N_2O$: C, 84.11; H, 4.83; N, 5.16; O, 5.90. Found C, 84.04; H, 4.75; N, 5.10; O, 5.83 %

VI u: IR (KBr, V max, cm^{-1}): 3461.00 (-OH stretching), 1499.53 (Ar C=C stretching), 1300.68 (C-N stretching), 1251.02 (C-C stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.1 [t, 3H,-CH_3], 7.3-7.5 [m, 5H, Ar-ring], 8.2 [s, -OH], **MS**: m/z 289 (M^+), Anal Calcd for $C_{20}H_{15}NO$: C, 83.59; H, 5.96; N, 4.87; O, 5.57. Found C, 83.57; H, 5.93; N, 4.85; O, 5.50 %

VI v: IR (KBr, V max, cm^{-1}): 3468.44 (-OH stretching), 2971.03 (-CH_3 stretching), 1662.06 (Ar C=C stretching), 1385.00 (C-N stretching), 1248.99 (C-C stretching), 1100.10 (C-O stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.1 [t, 3H,-CH_3], 7.2-7.9 [m, 5H, Ar-ring], 8.11 [s, -OH], **MS**: m/z 352(M^+), Anal Calcd for $C_{25}H_{17}NO$: C, 79.98; H, 5.43; N, 4.44; O, 10.15. Found C, 79.95; H, 5.42; N, 4.46; O, 10.13 %

VI w: IR (KBr, V max, cm^{-1}): 1535.00 (-NO_2 stretching), 3469.11 (-OH stretching), 1675.06 (Ar C=C stretching), 1381.02 (C-N stretching), 1258.89 (C-C stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.12 [t, 3H,-CH_3], 7.2-7.3 [m, 5H, Ar-ring], 8.5 [s, -ON_2], 8.19 [s, -OH], **MS**: m/z 395 (M^+), Anal Calcd for $C_{25}H_{16}N_2O_3$: C, 71.69; H, 4.43; N, 8.80; O, 15.08. Found C, 71.67; H, 4.40; N, 8.82; O, 15.14 %

VI x: IR (KBr, V max, cm^{-1}): 3471.10 (-OH stretching), 1680.76 (Ar C=C stretching), 1371.82 (C-N stretching), 1268.89 (C-C stretching), **^{1}H-NMR** (DMSO, δ ppm): 2.15 [t, 3H,-CH_3], 7.7-7.9 [m, 5H, Ar-ring], 8.1 [s, -OH], **MS**: m/z 366 (M^+), Anal Calcd for $C_{25}H_{17}NO_2$: C, 78.87; H, 5.23: N, 4.84; O, 11.06. Found C, 78.85; H, 5.20: N, 4.86; O, 11.09 %

VI y: IR (KBr, V max, cm^{-1}): 3469.30 (-OH stretching), 1661.96 (Ar C=C stretching), 1390.62 (C-N stretching), 1250.89 (C-C stretching), **^{1}H-NMR** (DMSO-*d*6, δ ppm): 2.5 [t, 3H,-CH_3], 7.2-7.9 [m, 5H, Ar-ring], 8.09 [s, -OH], **MS**: m/z 368 (M^+), Anal Calcd for $C_{25}H_{17}NO_2$: C, 78.87; H, 5.23: N, 4.84; O, 11.06. Found C, 78.85; H, 5.20: N, 4.86; O, 11.09 %

PHARMACOLOGICAL EVALUATION

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical

Committee (IAEC) of College, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), Government of India.

Registration number and date of registration

648/02/c/CPCSEA date: 30/09/2003

Toxicity Study[5]

The SD or Wister rats of either sex of weight 190-210 g were selected. Animals were housed standard condition of temperature 22° (± 3° C) and relative humidity (30-70%) with 12:12 light: dark cycle. The animals were fed with standard diet (pellets) and water ad libitum.

Acute toxicity was determined in rats by employing various logarithmic doses administered by oral route. Each group contained six wistar rats were orally administered with 10 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg and 100 mg/kg of synthesized compounds and kept in polystyrene cages. Behavioral changes were recorded at the interval of 30 min. for 4 h and also mortality after 24 h was recorded. One group was used as a control receiving only 1% w/v solution of tween 80 and calculated LD_{50}.

All the compounds synthesized were tested for acute toxicity test. No toxicity was observed at the doses of 10, 20, 40, 80, 100 mg/kg of body weight. It was observed no animal was died at the dose of 100 mg/kg of body weight.

Analgesic activity[6]

The analgesic activity of all the test compounds was evaluated by using Hot Plate Method and the instrument used for this purpose was Eddy's hot plate.

The albino mice having body weight 20-25 g were divided into twenty seven groups with six animals per cage. The first group was for control, second group for standard drug (Tramadol) and rest of twenty five groups were for the synthesized compounds. The solutions of the test compounds were prepared in Tween 80 (1 % w/v).

The test and standard compound were administered orally at dose of 20 mg/kg. The basal reaction time, for jump response and paw liking , when animals placed on hot plate (maintained at constant temperature of 55°C) was observed and reaction time of animals on hot plate at 0, 0.5, 1.0 and 1.5 hour after administration of the test and standard compounds, was also noted. The percent increase in reaction time (as an index of analgesia) after 1.5 hour was calculated and reported in **Table 3**. Comparison of the analgesic activities exhibited by the test and standard drug is shown in fig. 1.

% inhibition = [1-(before treatment /after treatment)] x 100

TABLE 3: PERCENT ANALGESIA OF THE TEST AND STANDARD DRUG (VI a-y)

Test compounds	Mean latency		% Inhibition
	Initial	After 1.5 hour	
Control	1.11 ± 0.32	1.60 ± 0.47	-
Standard (Tramadol)	4.51 ± 0.83	6.39 ± 0.89	69.57 ± 0.65
VI a	1.72 ± 0.12	4.92 ± 0.16	33.95 ± 0.85
VI b	1.32 ± 0.20	4.01 ± 0.26	31.91 ± 0.48
VI c	1.65 ± 0.15	3.02 ± 0.23	53.63 ± 0.85
VI d	1.44 ± 0.25	4.65 ± 0.25	29.96 ± 0.75
VI e	1.89 ± 0.14	5.05 ± 0.24	36.42 ± 0.89
VI f	1.77 ± 0.26	2.98 ± 0.32	58.39 ± 0.56
VI g	1.57 ± 0.25	2.84 ± 0.26	54.28 ± 0.67
VI h	1.28 ± 0.15	4.41 ± 0.32	28.02 ± 0.68
VI i	1.45 ± 0.23	4.65 ± 0.79	30.18 ± 0.45
VI j	1.32 ± 0.14	3.84 ± 0.26	33.37 ± 0.42
VI k	1.62 ± 0.24	2.69 ± 0.25	59.22 ± 0.36
VI l	1.55 ± 0.21	2.87 ± 0.35	53.00 ± 0.65
VI m	1.10 ± 0.26	3.97 ± 0.25	26.70 ± 0.85
VI n	1.47 ± 0.23	4.56 ± 0.25	31.23 ± 0.49

VI o	1.42 ± 0.15	4.87 ± 0.24	28.15 ± 0.86
VI p	1.55 ± 0.24	3.78 ± 0.15	40.00 ± 0.87
VI q	1.68 ± 0.14	4.12 ± 0.32	39.77 ± 0.88
VI r	1.13 ± 0.26	4.33 ± 0.25	25.09 ± 0.76
VI s	1.44 ± 0.24	4.98 ± 0.24	27.91 ± 0.81
VI t	1.38 ± 0.26	4.37 ± 0.25	30.57 ± 0.46
VI u	1.65 ± 0.24	3.82 ± 0.16	42.19 ± 0.65
VI v	1.84 ± 0.32	3.96 ± 0.26	45.46 ± 0.58
VI w	1.19 ± 0.34	4.44 ± 0.23	25.80 ± 0.48
VI x	1.33 ± 0.15	4.67 ± 0.25	27.47 ± 0.62
VI y	1.42 ± 0.16	5.01 ± 0.24	27.34 ± 0.74

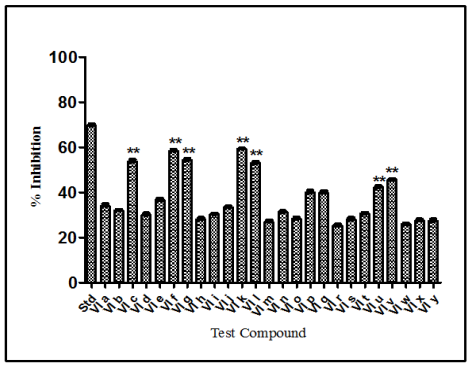


FIGURE 1: ANALGESIC ACTIVITY OF SYNTHESIZED COMPOUNDS (VI a-y)

Note: Analgesic activities of the test compounds were compared w.r.t control. Data are expressed as % analgecic activity ± S.E.M. (n = 6) and analyzed by one-way ANOVA followed by Bonferroin t test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when P < 0.01. All statistical calculations were carried out using Graph Pad® Prism 5.0 (USA) statistical software

Anti-inflammatory activity[6]

The anti-inflammatory activity of all the test compounds was evaluated by Carrageenan-Induced Rat Paw Edema Method.

Male or female Sprague-Dawley rats with a body weight between 100-120 g were divided into twenty seven groups with six animals per cage. The animals were starved overnight. To insure uniform hydration, the rats receive 5 ml of water by stomach tube (controls) or the test drug (50 mg/Kg) and standard drug (Diclofenac sodium) (50 mg/Kg) dissolved or suspended in the same volume. One hour later, the rats were challenged by a subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the plantar side of the left hind paw. The paw volume was measured by Vernier caliper scale immediately after injection, again after 5 hrs. The percent increase in paw volume (as an index of inflammation) after 5 hour was calculated and reported in **Table 4.** Comparison of the anti-inflammatory activities exhibited by the test and standard drug is shown in fig. 2.

The percent inhibition of rat paw edema was calculated by the following formula-

% inhibition = 1- [a-x/b-y] x 100

Where,

a = Paw volume of test group after 5 hrs of injecting carrageenan.

x = Paw volume of test group before injecting carrageenan.

b = Paw volume of control group after 5 hrs of injecting carrageenan.

y= Paw volume of control group before of injecting carrageenan.

TABLE 4: ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS (VI a-y)

Test compounds	Paw Volume (mm)		% Inhibition
	Initial	After 5 hrs	
Control	3.68 ± 0.61	6.18 ±	-
Standard (Diclofenac sodium)	4.48 ± 0.58	5.07 ± 0.34	87.36
VI a	3.12 ± 0.12	5.80 ± 0.25	52.79
VI b	2.98 ± 0.45	4.73 ± 0.54	62.00 ± 0.21
VI c	3.33 ± 0.56	5.23 ± 0.87	62.67 ± 0.35
VI d	2.88 ± 0.84	6.20 ± 0.67	45.45 ± 0.56
VI e	2.84 ± 0.65	4.06 ± 0.58	68.95 ± 0.48
VI f	2.59 ± 0.54	4.91 ± 0.75	51.74 ± 0.68
VI g	2.95 ± 0.45	5.82 ± 0.48	49.68 ± 0.58
VI h	2.72 ± 0.65	5.03 ± 0.75	53.07 ± 0.48
VI i	2.70 ± 0.25	5.60 ± 0.68	47.21 ± 0.98
VI j	3.26 ± 0.85	5.30 ± 0.35	60.50 ± 0.68
VI k	2.89 ± 0.45	6.22 ± 0.15	45.46 ± 0.58
VI l	2.69 ± 0.65	6.42 ± 0.24	40.90 ± 0.65
VI m	2.65 ± 0.35	5.78 ± 0.45	44.84 ± 0.58
VI n	3.01 ± 0.85	4.95 ± 0.56	59.80 ± 0.59
VI o	2.65 ± 0.47	4.78 ± 0.57	54.43 ± 0.68
VI p	3.21 ± 0.67	5.12 ± 0.59	61.69 ± 0.58
VI q	3.48 ± 0.51	6.54 ± 0.84	52.21 ± 0.27
VI r	2.82 ± 0.59	5.50 ± 0.57	50.27 ± 0.45
VI s	2.75 ± 0.56	5.96 ± 0.45	45.14 ± 0.65

VI t	2.59 ± 0.25	5.40 ± 0.57	46.96 ± 0.78
VI u	2.75 ± 0.49	4.94 ± 0.58	54.66 ± 0.68
VI v	3.44 ± 0.47	6.49 ± 0.59	52.00 ± 0.48
VI w	3.28 ± 0.48	5.60 ± 0.65	57.57 ± 0.65
VI x	2.96 ± 0.56	5.04 ± 0.45	57.73 ± 0.25
VI y	3.22 ± 0.65	5.34 ± 0.36	59.29 ± 0. 12

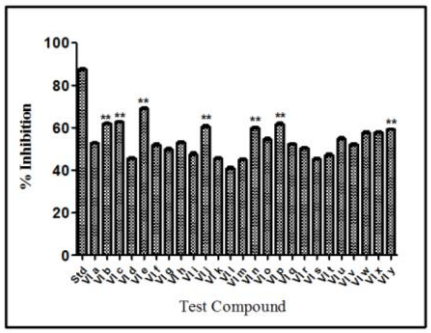


FIGURE 2: ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS (VI a-y)

Note: Anti-inflammatory activities of the test compounds were compared w.r.t control. Data are expressed as % anti-inflammatory activity ± S.E.M. (n = 6) and analyzed by one-way ANOVA followed by Bonferroin t test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when P < 0.01. All statistical calculations were carried out using Graph Pad® Prism 5.0 (USA) statistical software.

RESULTS AND DISCUSSION

The 2-[substituted phenyl]-4-substituted benzo[*f*]quinoline derivatives were successfully prepared by given scheme and further recrystallized by using ethanol and checked the purity by thin layer chromatographic techniques. The title compounds were further characterized by R_f value, melting point, FTIR, ^{1}HNMR and mass spectra. The synthesized compounds could be obtained in good yields with sharp melting points.

The structures of synthesized compounds were confirmed on the basis of spectral data. FTIR spectra of all synthesized compounds shows aromatic C=C stretching vibrations at about 1680-1650 cm-1 indicates presence of aromatic ring, All compounds shows absorbance band at range 1390-1339 cm-1 associated with the C-N stretching vibration. All the compounds shows the absorbance band at about 1298-1240 cm^{-1} associated with the stretching vibration of C-C bond .

The **comp. VI a, b, f, g, h, i, j, k, l, p, q, r, s, t, u** and **v** show strong band at 2980-2930 cm^{-1} stretching vibration indicates the presence of $–CH_3$ group, **comp. VI c, h, k, l, m, n, o, r** and **w** shows strong band at 1545-1525 cm^{-1} stretching vibration indicates the presence of $–NO_2$ group, **comp. VI d, e, i, j, n, o, s, t, u, v, w, x** and **y** shows strong band at 3472-3450 cm^{-1} stretching vibration indicates the presence of –OH group and **comp. VI b, g, l, q** and **v** shows strong band at 1100-1080 cm^{-1} stretching vibration indicates the presence of C-O bond.

The ^{1}HNMR spectrum of all synthesized compounds exhibited sharp muliplates peak cluster in the range of 6.9 -7.6 ppm indicating the presence of aromatic hydrogen.

The results of analgesic and anti-inflammatory activity of test compounds were given in Table 3 and 4 shows that **comp. VI c, f, g, k, l, u,** and **v** showed significant analgesic and **comp. VI b, c, e, j, n, p,** and **y** showed significant anti-inflammatory activity with compare to standard drugs Tramadol and Diclofenac sodium respectively.

CONCLUSION

A new series of 2-[substituted phenyl]-4-substituted benzo[*f*]quinoline were synthesized using appropriate synthetic route and screened them for analgesic and anti-inflammatory activity. It can be concluded that, the **comp. VI c, f, g, k, l, u,** and **v** showed significant analgesic activity with compared to standard drug Tramadol and **comp. VI b, c, e, j, n, p,** and **y** showed the significant anti-inflammatory activity with compared to the standard drug Diclofenac sodium. Thus research work was undertaken that the substitution of electron withdrawing group on phenyl ring enhance both activity. The encouraging results showed that the synthesis of 2-[substituted phenyl]-4-substituted benzo[*f*]quinoline may lead to the further development of novel analgesic and anti-inflammatory agent explored further.

ACKNOWLEDGEMENT

Authors are thankful to the Principal, J. L. Chaturvedi College of Pharmacy, Nagpur.

REFERENCES

1. Campose PJ et.al. Synthesis of benzoquinoline by the irradiation of 3-amino-2-alkene imines. Tetrahedron. 1958; (54): 6929-38.
2. Bhargava G, Mohan C, Mahajan MP. Lewis acid promoted imino Dials Alder reactions of 5-dieny pyrimidinones with N-aryl/naphthyl imines: synthesis of novel quinoline/benzoquinoline derivatives. Tetrahedron. 2008; (64): 3017-24.
3. Grachek VI. Synthesis of benzo[*f*]quinoline derivatives by condensation of N-arylmethylene-2-napthylamines with acetylcyclohexane and 1-acetylcyclohexene. Russian J Org Chem. 2004; 74(11): 1748-1755.
4. Furniss BS, Hannaford AJ, Smith PG, Tatchell AR. Vogel's Textbook of Practical Organic Chemistry. 5th ed. England: Longman Scientific and Technical; 1996. p. 236,199,256.
5. OECD (2000), Guidance Documents on Acute Oral Toxicity, Environmental Health and safety Monograph Series on Testing and Assessment No. 24.
6. Vogel HG et al. Drug Discovery and evaluation pharmacological assay. 2nd ed. New York: Springer-Verlag Berlin Heidelberg; 2002. p.696, 759.