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Synthesis and characterization of some novel derivatives of 6-fluoro-3-[3-(4-fluorophenyl)-1-isoproplyl indol-2-yl) allyl] piperidine-4-benzisoxazoles possessing good anti-inflammatory and antimicrobial activity

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ABSTRACT

The synthesis of a series of substituted 6-fluoro-3-[3-(4-fluorophenyl)-1-isoproplyl indol-2-yl) allyl] piperidine-4-benzisoxazole described which are novel and obtained in excellent yield. Substituted 3-(4-flourophenyl)-1-isopropyl indole 3a-h on condensation with acrolein gives substituted 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde which on again condensation with another active pharmaceutical ingredient i.e. 6-fluoro-3-(piperidine-4-yl) benzisoxazole which is neuroleptic active to give another biologically more potent compound which is substituted 6-fluoro-3-[3-(4-fluorophenyl)-1-isoproplyl indol-2-yl) allyl] piperidine-4-benzisoxazole 5a-h. All these novel compounds 5a-h have been characterized by spectroscopic means and have been screened for anti-inflammatory and antimicrobial activity.

KEYWORDS

Indole;
Derivative of indole;
Anti-inflammatory;
Antimicrobial activity.

INTRODUCTION

Indoles are abundant heterocyclic compound in nature. Indole and its derivative have captured the imagination of organic chemist for more than a centaury. At the beginning of twentieth century, a large number of naturally occurring compounds like alkaloids were found to possess indole nucleus. Indoles, both naturally-occurring and synthetic are of immense importance as biologically active alkaloids, and pharmaceutical agents [1-4]. Indole myriad derivatives have diverse pharmacological properties[5-8] like antimicrobial, anticancer, antihypertension, anti-inflammatory activity, which makes indole derivatives an important class of hetocyclic compounds. Due to the interesting chemical properties of indole it inspired chemist to design and synthesize a variety of indole derivatives[9].

The introduction of fluorine atoms, particularly into an organic compound can bring remarkable changes in the physical, chemical and biological properties, making them suitable for different applications in the areas of material science, agrochemicals and pharmaceuticals[10-14]. 1,2-benzisoxazole derivatives are widely used as analgesic[15], anticonvulsant[16,17], antipscyhotic[18,19] and as antimicrobial[20] agents. In view of these it was thought of interest to envisage preparing biologically potent new indole derivatives carrying fluorine atom and benzisoxazole moiety.

In this present study, we have synthesized some novel indole derivatives which contains fluorine and

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benzisoxazole moiety which is obtained by the condensation of 6-fluoro-3-(piperidine-4-yl) benzisoxazole which is antipsychotic agent[21] with substituted 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde to obtained a molecule which is biologically more potent and novel. All the synthesized novel compounds were characterized by their physical and spectral data (IR, ^{1}H NMR, Mass and elemental analysis). These compounds were also evaluated for their anti-inflammatory and antimicrobial activity.

RESULT AND DISCUSSION

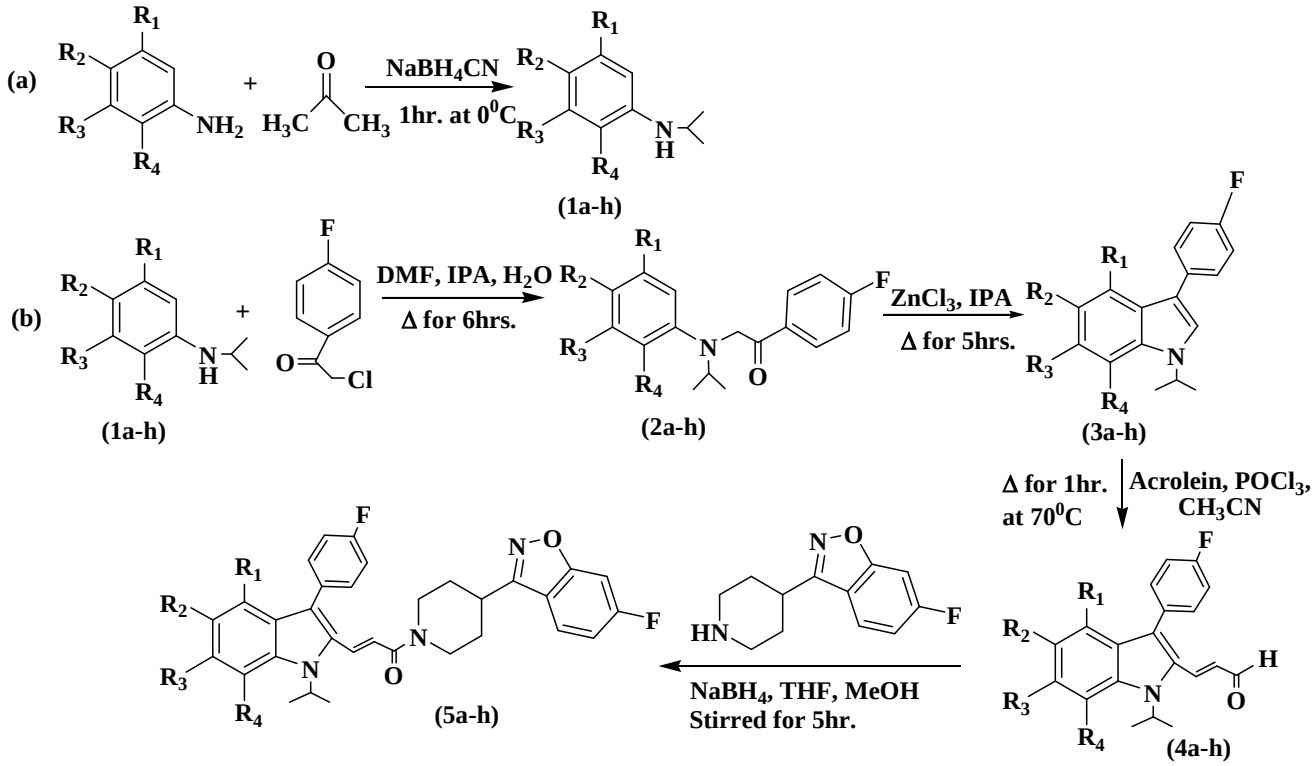
The aim of the present work was to synthesized and evaluates pharmacological active series of substituted 6-fluoro-3-[3-(4-fluorophenyl)-1-isoproplyl indol-2-yl) allyl] piperidine-4-benzisoxazole 5a-h (SCHEME 1) which are obtained by the condensation of substituted 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde **(4a-h)** with 6-fluoro-3-(piperidine-4-yl) benzisoxazole. The 4a-h was prepared from acrolein and Substituted 3-(4-flourophenyl)-1-isopropyl indole **(3a-h)** (SCHEME 1). The physical and spectral Characterisation data of compounds **(5a-h)** are given in TABLE 1. Further, the compounds were tested for anti-inflammatory, antibacterial and antifungal activities. All the compounds exhibited significant anti-inflammatory activity. Similarly maximum of the compounds shows moderate to significant potent antibacterial and antifungal activities.

Anti-inflammatory studies

The anti-inflammatory activities of **(5a-h)** (**TABLE** 2) were studied *in-vivo* for their percent inhibition of oedema in the carrageenan model of inflammation in rats using the method illustrated by Winter et al[24,25]. The percent inhibition of oedema was calculated against the control on the basis of experimental data obtained. All the compounds exhibited anti-inflammatory activity. Compounds **(5b)**, **(5c)** and **(5g)** showed activity comparable to standard drug indomethacin and the remaining compounds showed lower activity.

Antimicrobial activity

All the novel synthesized compounds were screened for their antimicrobial activity in *vitro* at doses of 100µg in 0.1ml of DMF against the bacteria *Escherichia coli*, *Bacillus cirroflagellosus* and *Salmonella typhi* using norfloxacin as standard and for their antifungal activity



SCHEME 1

in *vitro* against the fungi Aspergillus niger, Rhizoctonia bataticola and Penicillium using Griseofulvin as standard and DMF was used as culture medium and the method employed was cup-plate method[22,23]. The zone of inhibition was measured in mm and was compared with standard drugs. Norfloxacin showed a zone of inhibition (28mm) against bacterium *Escherichia coli* and of 25mm against *Bacillus cirroflagellosus* and 30mm against *Salmonella typhi*.

The investigation of antibacterial screening revealed that compounds **(5b, 5c, 5g, 5h)** are highly active against *E.coli* where as **(5b**, **5c)** and **(5g)** are highly active against *B. cirroflagellosus* and *Salmonella typhi* respectively. Compounds **(5a, 5d, 5e)** were moderately

TABLE 1: Physical constant and spectral data of compounds (5a-h)

Compd.	R_1	R_2	R_3	R_4	mp (b.p.) ^{0}C	Yield %	IRcm^{-1}	^{1}H NMR δ
(5a)	H	H	H	H	142-145	80	3060(aromatic C-H Str.), 2929(aliphatic C-H Str.), 1600, 1610(C=C & C=N), 1520(C-N Str.), 1375(C-O)	1.66-1.68(d, 6H, $2CH_3$), 2.04-2.18(m,6H, piperidine ring),2.96-2.99(d, 2H,piperidine ring), 3.05-3.11(m, 1H, piperidinering), 3.18-3.19(d, 2H, methine), 4.84-4.87(m, 1H, methine), 5.80-5.88(m, 1H, ethylene), 6.57-6.61(d, 1H, ethylene), 7.03-7.13 (m, 4H, benzene), 7.17-7.23(t, 1H, benzene), 7.25-7.27(d,1H, benzene), 7.38-7.43(m, 2H, indole), 7.50-7.56(t, 2H,indole), 7.69-7.73(m,1H, benzene).
(5b)	H	Br	H	H	97	85	3055(aromatic C-H Str.), 2925(aliphatic C-H Str.), 1595, 1611(C=C & C=N), 1522(C-N Str.), 1365(C-O)	1.72(d, 6H, $2CH_3$), 2.18-2.22(m, 6H, piperidine ring), 2.92-3.13(m, 3H, piperidine ring), 3.30-3.35 (d, 2H, methyl groupattached to piperidine ring), 5.08-5.20(septet, 1H, methineattached to two methyl groups), 5.90-6.08(m, 1H, ethylene attached to isoxazole), 6.62-6.66(d, 1H, ethylene attached to indole), 7.15-7.29(m, 4H, attached to fluorobenzene), 7.30-7.42(m, 2H, benzene of isoxazole), 7.50-7.61(m, 2H, indolering), 7.67(d, 1H, indole ring), 7.89-7.95(m, 1H, benzene of isoxazole).
(5c)	H	Cl	H	H	184	90	3045(aromatic C-H Str.), 2985(aliphatic C-H Str.), 1605, 1615(C=C & C=N), 1525(C-N Str.), 1370(C-O)	1.70.(d, 6H, $2CH_3$), 2.16-2.20(m, 6H, piperidine ring), 2.89-3.10(m, 3H, piperidine ring), 3.30-3.33(d, 2H, methyl group attached to piperidine ring), 5.07-5.22(septet, 1H, methine attached to two methyl groups), 5.92-6.07(m, 1H, ethylene attached to isoxazole), 6.60-6.63(d, 1H, ethylene attached to indole), 7.15-7.30(m, 4H, attached to fluorobenzene), 7.31-7.44(m, 2H, benzene of isoxazole), 7.51-7.62(m, 2H, indole ring), 7.60(d, 1H, indole ring), 7.88-7.91(m, 1H, benzene of isoxazole).
(5d)	C_2H_5	H	H	H	158	85	3040(aromatic C-H Str.), 2935(aliphatic C-H Str.), 1595, 1615(C=C & C=N), 1510(C-N Str.), 1360(C-O)	1.22(t, 3H, methyl of ethyl group), 1.68-1.69.(d, 6H, $2CH_3$), 1.99-2.16(m, 6H, piperidine ring), 2.66(q, 2H, CH_2 of ethylene), 2.92-2.95(m, 2H, piperidine ring), 3.29-3.40(d, 2H, methyl group attached to piperidine ring), 5.10-5.15(septet, 1H, methine attached to two methyl groups), 5.90-5.98(m, 1H, ethylene attached to isoxazole), 6.60-6.65(d, 1H, ethylene attached to indole), 7.00-7.19(m, 4H, attached to fluorobenzene), 7.27-7.31(t, 1H, benzene of isoxazole), 7.39-7.44 (d, 1H, benzene of isoxazole), 7.60-7.90(m, 3H, indole ring), 7.93-7.95(m, 1H, benzene of isoxazole), 3.00-3.16(m, 1H, piperidine ring),

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TABLE 1: Physical constant and spectral data of compounds (5a-h)

Compd.	R_1	R_2	R_3	R_4	mp (b.p.) ^{0}C	Yield %	IRcm^{-1}	^{1}H NMR δ
(5e)	H	C_2H_5	H	H	162	82	3060(aromatic C-H Str.), 2925(aliphatic C-H Str.), 1600, 1612(C=C & C=N), 1520(C-N Str.), 1365(C-O)	1.20(t, 3H, methyl of ethyl group), 1.69.(d, 6H, $2CH_3$), 2.00-2.12(m, 6H, piperidine ring), 2.63(q, 2H, CH_2 of ethylene), 2.90--2.93(m, 2H, piperidine ring), 3.01-3.11(m,1H, piperidine ring), 3.20-3.33(d, 2H, methyl group attached to piperidine ring), 5.03(septet, 1H, methine attached to two methyl groups), 5.92-6.05(m, 1H, ethylene attached to isoxazole), 6.60-6.63(d, 1H, ethylene attached to indole), 7.12-7.20(m, 4H, attached to fluorobenzene), 7.22-7.29(t, 1H, benzene of isoxazole), 7.31-7.33(d, 1H, benzene of isoxazole), 7.37-7.40(m, 2H, indole ring), 7.59 (d, 1H, indole ring) 7.66-7.70(m, 1H, benzene of isoxazole).
(5f)	H	NO_2	H	H	151	92	3062(aromatic C-H Str.), 2945(aliphatic C-H Str.), 1580, 1600(C=C & C=N), 1510(C-N Str.), 1380(C-O)	1.65-1.69.(d, 6H, $2CH_3$), 2.15-2.20(m, 6H, piperidine ring), 2.88-3.02(m, 3H, piperidine ring), 3.21-3.28(d, 2H, methyl group attached to piperidine ring), 4.89-4.93(septet, 1H, methine attached to two methyl groups), 5.88-5.97(m, 1H, ethylene attached to isoxazole), 6.60-6.63(d, 1H, ethylene attached to indole), 7.12-7.28(m, 4H, attached to fluorobenzene), 7.31-7.45(m, 2H, benzene of isoxazole), 7.60-7.66(m, 2H, indole ring), 7.69(d, 1H, indole ring), 7.86-7.91(m, 1H, benzene of isoxazole).
(5g)	H	F	H	H	141	95	3060(aromatic C-H Str.), 2948(aliphatic C-H Str.), 1595, 1616(C=C & C=N), 1520(C-N Str.), 1364(C-O)	1.69-1.71.(d, 6H, $2CH_3$), 2.17-2.20(m, 6H, piperidine ring), 2.88-3.20(m, 3H, piperidine ring), 3.35-3.37(d, 2H, methyl group attached to piperidine ring), 5.10-5.25(septet, 1H, methine attached to two methyl groups), 5.90-6.05(m, 1H, ethylene attached to isoxazole), 6.70-6.73(d, 1H, ethylene attached to indole), 7.15-7.38(m, 4H, attached to fluorobenzene), 7.43-7.48(m, 2H, benzene of isoxazole), 7.55-7.69(m, 2H, indole ring), 7.66-7.69(d, 1H, indole ring), 7.80-7.86(m, 1H, benzene of isoxazole).
(5h)	H	OH	H	H	174	87	3064(aromatic C-H Str.), 2984(aliphatic C-H Str.), 1602, 1614(C=C & C=N), 1524(C-N Str.), 1366(C-O)	1.74.(d, 6H, $2CH_3$), 2.20-2.23(m, 6H, piperidine ring), 2.90-3.10(m, 3H, piperidine ring), 3.30-3.32(d, 2H, methyl group attached to piperidine ring), 5.10-5.23(septet, 1H, methine attached to two methyl groups), 5.94-6.16(m, 1H, ethylene attached to isoxazole), 6.63-6.90(d, 1H, ethylene attached to indole), 7.26-7.37(m, 4H, attached to fluorobenzene), 7.42-7.49(m, 2H, benzene of isoxazole), 7.55-7.59(m, 2H, indole ring), 7.70(d, 1H, indole ring), 7.80-7.83(m, 1H, benzene of isoxazole).

active towards *E.coli* and compounds **(5a**, **5c**, **5e)** showed moderate activity towards B. cirroflagellosus. Rests of the compounds were weakly active towards all the bacteria's. The investigation of antifungal activity data revealed that compounds **(5a, 5b, 5c, 5g)** and **(5h)** shows inhibitory effect against *A.niger* and *Penicillium*. Similarly compounds **(5c, 5d, 5e, 5f, 5g)** and **(5h)** shows inhibitory effect against *R.bataticola*. Remaining compounds are inactive against all the fungus result shown in TABLES 3 and 4 respectively.

TABLE 2 : Anti-inflammatory activity of compounds (5a-h)

Compd.	V_t-V_o (Mean±SEM)	% inhibition of oedema at the end of 3 hr.
Indomethacin	0.133±0.012	75.04^{+}
(5a)	0.100±0.003	81.23*$^{+}$
(5b)	0.134±0.009	74.85^{+}
(5c)	0.200±0.033	62.47^{+}
(5d)	0.400±0.040	24.95*$^{+}$
(5e)	0.333±0.021	37.52*$^{+}$
(5f)	0.300±0.019	43.71*$^{+}$
(5g)	0.113±0.004	74.85^{+}
(5h)	0.230±0.021	56.28*$^{+}$

Values expressed as Mean±SEM, n= 6 in each group, *P<0.05 compared with indomethacin, $^{+}$P<0.05 compared with control.

TABLE 3 : Antibacterial screening results of the compounds (5a-h)

Comp.	Antibacterial activity zone inhibition		
	E.coil	*B.cirroflagellosus*	*Salmonella typhi*
(5a)	++	++	+
(5b)	+++	+++	++
(5c)	+++	++	+++
(5d)	++	+	+
(5e)	++	++	+
(5f)	+	+	+
(5g)	+++	+++	+++
(5h)	+++	++	+

+ = weakly active (12-16mm), ++ = moderately active (17-21mm), +++ = highly active (22-30mm).

TABLE 4 : Antifungal screening results of the compounds (5a-h)

Comp.	Antifungal activity		
	A.niger	*R.bataticola*	*Penicillium*
5a	-ve	+ve	-ve
5b	-ve	+ve	-ve
5c	-ve	-ve	-ve
5d	+ve	-ve	+ve
5e	+ve	-ve	-ve
5f	+ve	-ve	+ve
5g	-ve	-ve	-ve
5h	-ve	-ve	+ve
Griseofulvin	-ve	-ve	-ve
control -	+ve	+ve	+ve

EXPERIMENTAL

Melting points (m.p.) were determined in open capillary tube and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600FT spectrometer at a ca. 5-15% solution in DMSO-d_6 or $CDCl_3$ (TMS as internal standard) GCMS was recorded on Perkin-Elmer clarus 500 mass spectrometer. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet lights (254nm). Physical constants and spectral characterization data of all the compounds reported in this paper are summarized in TABLE 1.

General procedure for the preparation of Isopropyl aniline (1a)

A mixture of aniline (0.161mmol) and acetone (0.161mmol) was taken into three necked round bottom flask in that $NaBH_4CN$ (0.322mmol) in 25ml of methanol was added under continuous stirring. When the starting material disappeared almost completely (after 1hr, checked by TLC), the reaction mixture was quenched with 10% HCl and neutralized with the base and the reaction product was extracted with ethyl acetate (25ml). The ethyl acetate extract was washed with brine and dried over Na_2SO_4 and concentrated under vaccume to obtained pure product.

Other compounds **(1b-h)** was prepared the similar way using various anilines. Characterization data are presented in TABLE 1.

Compound (1a): Yield 93%, m.p. low melting, (Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found, C, 79.93; H, 9.68; N, 10.35%), ^{1}H NMR: 1.22-1.28(d, 6H, $2CH_3$), 3.52-3.64(m, 1H, -CH), 6.23-7.52(m, 5H, Ar-H).

General procedure for the preparation of 2-(N-isopropyl- N-phenylamino)-1-(4-flourophenyl) ethanone (2a)

4-fluorophenacyl chloride (0.088mmol) was dissolved in 100ml of DMF in which isopropyl aniline **(1a)** (0.148mmol) was added with continious stirring. Reaction mixture was reflux for 6hrs. at 105^{0}C. After cooling to room temp., the reaction mixture was treated with water to obtained crude product. The solid obtained was filtered, washed with water and crystallized from isopropanol.

Other compounds **(2b-h)** was prepared the similar way using **(1b-h)** and 4-fluorophenacyl chloride. Characterization data are presented in TABLE 1.

Compound 2a: Yield 35%, m.p.80-82^{0}C, (Anal. Calcd for $C_{17}H_{18}FNO$: C, 75.25; H, 6.69; N, 5.16. Found, C, 75.23; H, 6.68; N, 5.15%), ^{1}H NMR: 1.17-1.23(d, 6H, $2CH_3$), 3.56-3.59(septet, 1H, -CH), 4.65(s, 2H, N-CH_2), 6.70-7.22(m, 4H, Ar-H), 7.31-7.50(m, 4H,

Ar-H of Flouro benzene).

General procedure for the preparation of 3-(4-flourophenyl)-1-isopropyl indole (3a)

To a solution of **(2a)** (0.044mmol) in isopropanol (100ml) was added $ZnCl_3$ (0.335mmol) and it was refluxed for 5hrs. After cooling to 10^0C, the reaction mixture was treated with dil. HCl followed by 200ml of DCM. The DCM layer was separated and washed with brine. The organic phase were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtained **(3a)**.

Other compounds **(3b-h)** was prepared the similar way using **(2b-h)**. Characterization data are presented in TABLE 1.

Compound 3a: Yield 60%, m.p.94-95^{0}C, (Anal. Calcd for $C_{17}H_{16}FN$: C, 80.60; H, 6.37; N, 5.53. Found, C, 80.61; H, 6.36; N, 5.54%), ^{1}H NMR: 1.50(d, 6H, $2CH_3$), 4.70(septet, 1H, -CH), 7.51(s, 1H, Ar-H of indole), 7.46-7.52(m, 2H, Ar-H of indole), 7.35-7.42(m, 2H, Ar-H of indole), 7.01-7.15(m, 4H, Ar-H of Flouro benzene).

General procedure for the preparation of 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylal dehyde (4a)

A mixture of $POCl_3$ (0.0403mmol) and acetonitrile (15ml) was cooled to -10^{0}C, to this acrolein (0.0308 mmol) in 10ml of acetonitrile was added slowly. Then the reaction mixture was brought to room temp and **3a** (0.0237mmol) in 10ml of acetonitrile was added with continious stirring. Reaction mixture was heated upto 70^{0}C for 1hr. After cooling it was quenched with distilled water followed by 100ml of DCM. The extracted layer was separated and concentrated to obtained solid product which was again extracted with toluene and charged with silica to obtained slurry. The obtained slurry was heated upto 45^{0}C and filtered, washed with toluene. The toluene layer dried over Na_2SO_4 and concentrated to obtained pure products **(4a)**.

Other compounds **(4b-h)** was prepared the similar way using **(3b-h)** and acrolein. Characterization data are presented in TABLE 1

Compound 4a: Yield 93%, m.p.122-124^{0}C, (Anal. Calcd for $C_{20}H_{18}FNO$: C, 78.15; H, 5.90; N, 4.56. Found, C, 78.13; H, 5.98; N, 4.55%), ^{1}H NMR: 1.60(d, 6H, $2CH_3$), 5.03(septet, 1H, -CH), 6.01-6.10 (dd, 1H, etylene attached to aldehyde), 7.68-7.70(d, 1H, etylene attached to benzene indole), 9.40-9.48(d, 1H, aldehydic proton), 7.49-7.56(m, 2H, Ar-H of indole), 7.40-7.44(m, 2H, Ar-H of indole), 7.00-7.20(m, 4H, Ar-H of Flouro benzene).

General procedure for the preparation of 6-fluoro-3-[3-(4-fluorophenyl)-1-isoproplyl indol-2-yl) allyl] piperidine-4-benzisoxazole (5a)

To a solution of **(4a)** (0.019mmol) in methanol (100ml) was taken in round bottom flask in this 6-fluoro-3-(piperidine-4-yl) benzisoxazole (0.0195mmol) was added with continious stirring. The reaction mixture was cooled to 10^{0}C and sodium borohydride (0.078mmol) was added in lot, after complete addition reaction mixture was brought to room temp. and stirred for 5hrs., then the reaction mixture was quenched with 10% HCl and neutralized with base. It was extracted with ethyl acetate, the extracted layer was washed with brine and dried over Na_2SO_4 and concentrated under vaccume to obtain the titled product **(5a)**.

Other compounds **(5b-h)** was prepared the similar way using **(4b-h)** and 6-fluoro-3-(piperidine-4-yl) benzisoxazole. Characterization data are presented in TABLE 1.

Compound 5a: Yield 80%, m.p.142-145^{0}C, (Anal. Calcd for $C_{32}H_{29}F_2N_3O_2$: C, 73.13; H, 5.56; N, 7.99. Found, C, 73.14; H, 5.55; N, 7.98%), ^{1}H NMR: 1.66-1.68(d, 6H, $2CH_3$), 2.04-2.18(m, 6H, piperidine ring), 2.96-2.99(d, 2H, piperidine ring), 3.05-3.11(m, 1H, piperidine ring), 3.18-3.19(d, 2H, methine), 4.84-4.87(m, 1H, methine), 5.80-5.88(m, 1H, etylene), 6.57-6.61(d, 1H, etylene), 7.03-7.13(m, 4H, benzene), 7.17-7.23(t, 1H, benzene), 7.25-7.27(d, 1H, benzene), 7.38-7.43(m, 2H, indole), 7.50-7.56(t, 2H, indole), 7.69-7.73(m,1H, benzene).

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REFERENCES

[1] R.J.Sundberg; 'Indoles', Academic Press, London, **(1996)**.

[2] J.E.Saxton; Nat.Prod.Rep., 559 **(1997)**.

[3] H.J.Borschberg; Curr..Org.Chem., **9**, 1465 **(2005)**.

[4] A.Kleeman, Engel, B.Kutscher, D.Reichert; 'Pharmaceutical Substances', 4th ed., Thieme, New York, **(2001)**.

[5] S.H.Abadi; Arch.Pharm., **22**, 352 **(1998)**.

[6] E.B.Skibo, C.Xing, R.J.Dorr; Med.Chem., **44**, 3535 **(2001)**.

[7] K.S.Pitzer, P.John; PCT Int Appl., WO 0018769; Chem.Abstr., **132**, 260669r **(2000)**.

[8] B.Zang, U.S.Pelaez; Pat.6081579, **(1999)**; Chem.Abstr., **132**, 266695w **(2000)**.

[9] G.W.Gribble; J.Chem.Soc., Perkin Tranz,.**1**, 1045-47 **(2000)**.

[10] **(a)** R.E.Banks, B.E.Smart, J.C.Tatlow; Organo fluorine Chemistry: Principles and Commercial Applications, Plenum, New York, NY, 2 **(1994)**.
(b) I.Ojima, J.R.McCarthy, J.T.Welch; Biomedical Frontiers of Fluorine Chemistry, ACS Symposium Series- American Chemical Society, Washington, DC, 639 **(1996)**.
(c) R.Filler; Organic Chemistry in Medicinal Chemistry and Biomedical Applications, Elsevier, Amsterdam, **(1993)**.
(d) J.T.Welch, S.Eswaraksrishnan; Fluorine in Bioorganic Chemistry, Wiley, New York, NY, **(1991)**.
(e) R.Filler, K.Kirk, M.Hudlicky, A.E.Pavlath; J. American Chem.Soc., Washington, DC, 187 **(1995)**.

[11] **(a)** A.J.Elliot; J.American Chem.Soc., Washington, DC, **(1995)**.
(b) V.A.Sholoshonok; Stereochemical Challenges and Biomedical Targets, Wiley, New York, NY, **(1999)**.

[12] **(a)** D.Cartwright, R.E.Banks, B.E.Smart, J.C. Tatlow; Principles and Commercial Applications, Plenum, New York, NY, **(1994)**.
(b) R.W.Lang; J.American Chem.Soc., Washington, 187 **(1995)**.

[13] B.E.Smart, R.E.Banks, J.C.Tatiow; Principles and Commercial Applications, Plenum, New York, NY, **(1994)**.

[14] **(a)** D.O.O'Hagan, H.S.Rzepa; J.Chem.Soc., 645 **(1997)**.
(b) J.D.Dunitz, R.Taylor; Chem.Eur.J., **3**, 89 **(1997)**.
(c) J.A.K.Howard, V.J.Hoy, D.O.O'Hagan, G.T. Smith; Tetrahedron, **52**, 12613 **(1996)**.

[15] H.Hasegawa; Curr.Med.Res., Opin., **20**, 577-80 **(2004)**.

[16] Y.Yasuda, Y.Utsui, Y.Sharashi, T.Karasawa, T.Yashida, Y.Shimizu; Epilepsia, **20**, 623-33 **(1979)**.

[17] Uno Hitoshi Kurukova Mikio, Masuda, Yoshinobu; J.Med.Chem., **22**, 180-83 **(1997)**.

[18] G.Vanden Bossche, Y.G.Gelders, S.L.Heylen; Acta Psiquiator Pscicol Am., **36**, 1325 **(1990)**.

[19] M.Shimuzu, K.Yoshida, T.Karasawa, M.Masuda, M.Oka; Expenentia, **30**, 405 **(1994)**.

[20] K.A.Thakar, B.M.Bhawal; Curr.Sci., **47**, 950-52 **(1978)**.

[21] T.S.Joseph, C.A.Richard, A.G.Beth, L.S.Blaine, S.Ulrich, J.G.Edward, C.J.Michael, B.E.Daniel, P.H.Francis, W.D.Robert; J.Med., Chem., **28**, 761-69 **(1985)**.

[22] F.Kavanagh; 'Analytical Microbiology', Academic Press, New York, 125 **(1963)**.

[23] H.W.Seeley, P.J.Van Denmark; Microbes in action: A laboratory Manual of Microbiology, D.B. Taraporevala Sons and Co.Pvt.Ltd., Bombay, 55-80 **(1975)**.

[24] C.E.Winter, E.A.Risley, G.W.Nuss; Proc.Soc.Exp. Bio.Med., **111**, 544 **(1962)**.

[25] R.Seshagiri, N.Murlidhar, M.U.R.Naidu, A.V. Junnarkar, P.P.Singh; Indian J.Expt.Biol., **29**, 120 **(1991)**.