IJPSR (2022), Volume 13, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 February 2022; received in revised form, 23 March 2022; accepted, 30 March 2022; published 01 April 2022

SYNTHESIS AND ANTI-CONVULSANT ACTIVITY OF NOVEL BENZHYDRYL PIPERAZINE DERIVATIVES

Kuldeep Singh [*1], Ashok K. Shakya [2], Shashi Alok [3], Rajashri R. Naik [2] and Arun Kumar [1]

Faculty of Pharmacy [1], Integral University Kursi Road, Lucknow - 226026, Uttar Pradesh, India.
Pharmacological and Diagnostic Research Centre [2], Faculty of Pharmacy, Amman University, Po Box 263, Amman - 19328, Jordan.
Institute of Pharmacy [3], Bundelkhand University, Jhansi - 284127, Uttar Pradesh, India.

Keywords:

Anticonvulsant, Benzhydryl piperazine, Piperazine, Neurotoxicity

Correspondence to Author:
Dr. Kuldeep Singh

Associate Professor,
Faculty of Pharmacy, Integral University Kursi Road, Lucknow - 226026, Uttar Pradesh, India.

E-mail: kuldeep@iul.ac.in

ABSTRACT: A series of 1 - (4 -Benzhydryl piperazin-1-yl) -3-(mono -substituted) propan-1-one (7c-i) and *N* - (substituted) - 2 - (4 –benz-hydrylpiperazin – 1 - yl) acetamide (7a, 7d) were designed, synthesized and evaluated for their anticonvulsant and neurotoxicity activity. The chemical structure of the synthesized compounds was elucidated by spectral and elemental analysis. Compounds like 7d, 7c, and 7g showed good anticonvulsant activity and less neurotoxicity. Compounds 7a, 7c, 7f and 7l produce more neurotoxicity and also have less protection against convulsive stimuli than the other compounds.

INTRODUCTION: Epilepsy is a chronic disease differentiated by the paroxysmal and reoccurring incidences of uncontrolled excitation of neurons of brain. Currently, 50 million individuals are affected by epilepsy [1, 2]. The recently discovered antiepileptic drugs have been reported for different seizures, including Phenytoin, carbamazepine, lamotrigine, sulfamate, and topiramate. The SAR for these kinds of agents is well reported in the literature, which suggests the need of two aryl binding sites at both ends and an important hydrogen binding site in the middle for potent activity. The pieces of evidence suggest that the diphenyl methyl attached to piperazine increases the anticonvulsant activity by providing the hydrophobicity to the molecule. The compounds prioritized for the anticonvulsant properties should have a C=O group required for hydrogen bonding interactions at the active site. The hydrophobic diphenyl moiety showed higher activity than other groups. The insertion of the $–CH_2-CH_2-N$ at one end with donor and acceptor group retained the activity.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(4).1777-84

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(4).1777-84

Pharmacological Screening: The compounds were tested for anticonvulsant activity using an electroshock seizure (MES) technique. Animals were exposed to submaximal electroshock for 0.2 seconds at 150 mA at 60 Hz, using standard auricular electrodes. All compounds were dissolved in DMSO. Rats were screened 24 h prior to the experiment. Only the rats showing the episodes of the convulsions were selected. The next day, the compounds were administered intra- peritoneally, and the rats were challenged to the electric shocks at 30 min and 4 h post-dose.

The test compound's ability to prevent MES-induced seizure spread/discharge across neural tissue was recorded as an increase in anticonvulsant activity, when the hind limb tonic extensor spasm was abolished. Electro-convulsiometer (Decibel Instrument, Model no. 5832) was used for the activity [3-7].

Neurotoxicity Screening: The rotarod test was used to evaluate neurotoxicity. The rotarod test measured minimal motor impairment in rats (Medicraft®, Lucknow, India). The rat was trained to stay on a 3.2 cm diameter knurled rod rotating at 6 revolutions per minute for 3 consecutive days. Only animals that had previously shown their capacity to stay on the spinning rod for at least one minute were considered for the test. A normal rat can stay on a rotating rod at this speed for an extended period. Test compounds were given i.p. to previously trained rats at dosages of 30, 100, and 300 mg/kg. The rat was placed on the spinning rod thirty minutes after i.p. treatment. The failure of the animal to stay on the rod for at least 1 minute in each of three attempts is regarded as neurological toxicity [7].

TABLE 1: EFFECT OF TESTED COMPOUNDS AND PHENYTOIN ON MAXIMAL ELECTROSHOCK INDUCED CONVULSIONS IN RAT (N=6)

Compd. code	Dose (mg/kg i.p.)	MES (number of animals protected)		NT (number of animals exhibited neurotoxicity)		ED_{50}** (mg/kg)	ED_{50} (mM)	Activity in comparison to Phenytoin
		½hr	4hr	½hr	4hr			
(7a)	30	2	2	0	0	143.6	0.317	0.13
	100	3	1	3	3			
	300	4	2	4	4			
(7c)	30	4	4	0	0	18.5	0.047	0.87
	100	5	5	3	3			
	300	6	6	4	4			
(7d)	30	3	1	0	0	21.7	0.049	0.84
	100	4	3	3	1			
	300	4	5	4	3			
(7f)	30	3	3	0	0	30.0	0.070	0.59
	100	5	5	3	3			
	300	6	6	4	4			
(7g)	30	4	5	0	0	18.5	0.045	0.9
	100	5	5	3	1			
	300	6	6	4	3			
(7h)	30	2	1	0	0	259.3	0.573	0.07
	100	3	1	3	1			
	300	3	1	4	3			
(7i)	30	1	3	0	0	208.6	0.447	0.09
	100	2	3	3	3			
	300	4	4	4	4			
Phenytoin	10	3	3	0	0	10.3#	0.041	1.0
	30	5	4	3	3			
	100	6	6	4	4			

* ED_{50} is calculated using XLSOFT (Version 2012.2.01) on the basis of maximum effect observed at ½ h. **. The values in the table indicate the minimum dose (mg/kg, b.wt.) required to demonstrate anticonvulsant activity in half or more of the rat. #ED_{50} (Choi, *et al.*, 1996) [8]

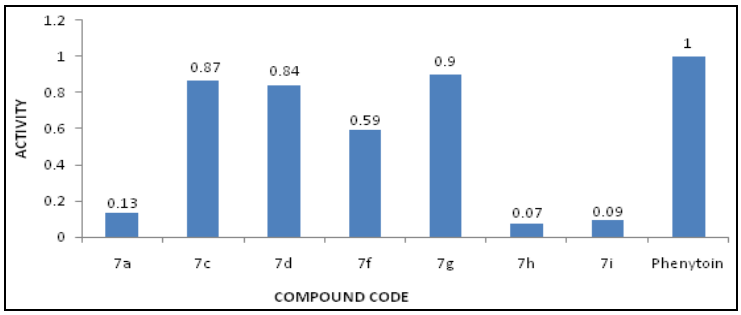


FIG. 1: GRAPHICAL PRESENTATION OF ANTICONVULSANT ACTIVITY OF SYNTHESIZED COMPOUNDS

Experimental Section:

MATERIALS AND METHODS: The melting points were recorded in open glass capillary tubes usingVeego melting point apparatus (Veego, Bombay, India) and are uncorrected.

Reactions were monitored by thin layer chromatography on silica gel G plates using various solvent systems, iodine vapours, and UV chamber to visualize spots.

Infrared (IR) spectra were recorded using a Perkin Elmer FTIR spectrometer.

Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DRX-400 and 300.

The text mentions the chemical shifts (δ, ppm) relative to TMS as an internal standard.

Spin multiplets are given as s (singlet), d (doublet), t (triplet), m (multiplet) and q (quartet). Mass spectra were recorded on the DART-MS and recorded on a JEOL-Accu TOF JMS-T100 LC mass spectrometer. Column chromatography was performed using Silica gel (60–120 mesh).

RESULTS AND DISCUSSION:

Chemistry: In the present studies, we have designed and synthesized the title compounds while keeping in mind that a number of clinically active anticonvulsants possess a heteroatomic system with a phenyl ring and electron donor system.

The structure of some title compounds (7a-i) fulfills all the pharmacophoric structural requirements, *i.e.,* presence of diphenyl group as hydrophobic portion, C=O as electron donor system, -NH-CO- or the terminal nitrogen as hydrogen bonding site and hydrophobic aryl ring responsible for metabolism [9, 10].

The key starting material (Z) were synthesized according to the published procedure (Meng T *et al.,* 2010).

The synthesis of compounds (7c, 7f, 7g, 7h and 7i) have been carried out as presented in **Scheme 1** and compound (7a, 7d) as presented in **Scheme 2.**

The intermediate compounds (3, 4 & 5y) were synthesized by the reaction of benzhydryl piperazine with the various acyl chlorides.

The intermediate compound (6) was synthesized by the reaction of benzhydryl piperazine and 1-bromo-2-chloro ethane, and the intermediate compound (k) was synthesized by the reaction of 1-bromo-3-chloro propane and benzhydryl piperazine.

The title compound 2 - (2 - (1*H*-indol – 3 - yl) ethylamino) – 1 - (4 – benzhydrylpiperazin – 1 - yl) ethanone (7h) was synthesized by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone (3) and tryptamine.

The compound 1-(4-benzhydrylpiperazin - 1 - yl) – 2 - (2, 3 – dihydro - 1*H* – inden – 5 - ylamino) ethanone (7f) was synthesized by refluxing of 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone (3) with the 5-AminoIndan.

The compound 3-(2-(1*H*-indol-3-yl)ethyl amino)-1-(4-benzhydryl piperazin-1-yl) propan-1-one (7i) was synthesized by the reaction of tryptamine and 1-(4-benzhydrylpiperazin - 1 - yl)- 3 - chloropropan – 1 - one (5), was synthesized by the reaction of tryptamine and 1-(4-benzhydrylpiperazin-1-yl)-4-chlorobutan-1-one (4).

The compound *N*-(2-(4-benzhydrylpiperazin-1-yl) ethyl)-2, 3-dihydro-1*H*-inden-5-amine (7g) was synthesized by refluxing of 1-benzhydryl-4-(2-chloroethyl) piperazine and 5-amino Indan.

The compound *N*-(2-(1*H*-indol-3-yl) ethyl)-3-(4-benzhydrylpiperazin-1-yl) propan-1-amine (7c) was synthesized by the refluxing of 1-benzhydryl-4-(3-chloropropyl) piperazine and tryptamine.

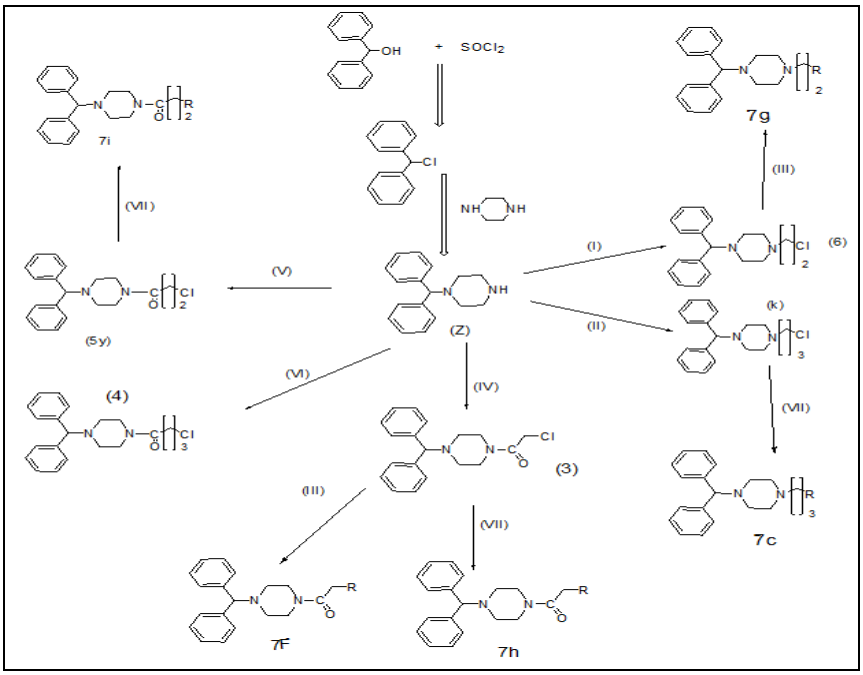
The compound *N*-(2-(1*H*-indol-3-yl) ethyl)-2-(4-benzhydrylpiperazin-1-yl) acetamide (7a) was synthesized by the reaction of *N*-(2-(1*H*-indol-3-yl) ethyl)-2-chloroacetamide and benzhydryl piperazine.

The compound 2-(4-benzhy-drylpiperazin – 1 - yl) – *N* - (quinolin – 8 -yl) acetamide (7d) was synthesized by refluxing of 2 – chloro – *N* - (quinolin – 8 - yl) acetamide and benzhydryl piperazine.

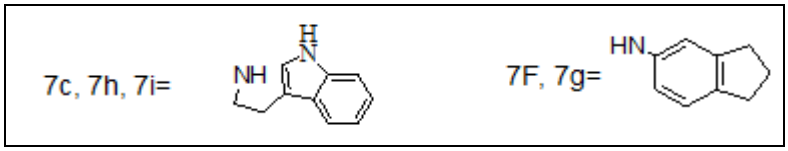
Progress of the reaction was checked by TLC, and their structures were confirmed by means of IR, ^{1}H-NMR, mass spectrometry, and elemental analysis.

Chemistry:

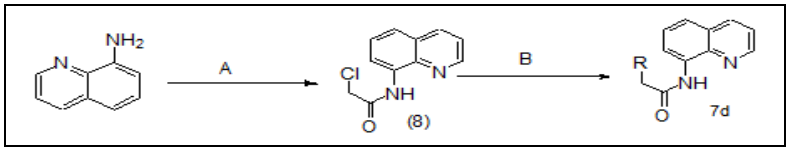
Reaction Scheme (1):



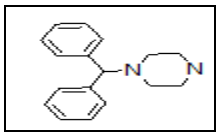
Where R=



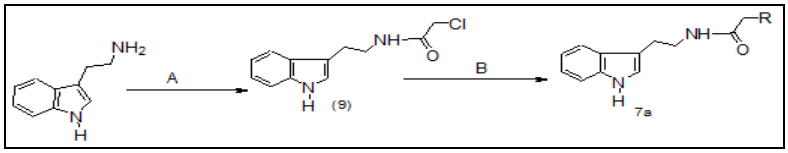
Reaction Scheme 2:



Where R=



Reaction Scheme 3:



Where R=

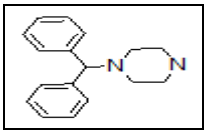


Fig. 2: Synthesis of Piperazine Derivatives. Reagent Conditions: - (I) $ClCH_2CH_2Br$, K_2CO_3, DMF, RT (II) $ClCH_2CH_2CH_2Br$, K_2CO_3, DMF, RT (III) 5-aminoIndan, Na_2CO_3, Ethanol, 12 h (IV) $ClCH_2COCl$, DCM, 0-5°C, TEA (V) $Cl(CH_2)_2$ COCl, dioxane, 0-5°C, RT ,6-12 h (VI) $Cl(CH_2)_3COCl$, dioxane, 0-5°C, RT ,6-12 h (VII) Tryptamine, K_2CO_3, DCM, 12 h (2)- DCM, $SOCl_2$, Piperazine, 40°C, 3h, CH_3CN (A) $ClCH_2COCl$, TEA, DCM (B) benzhydryl piperazine, K_2CO_3, DMF.

Synthetic Procedures and Characterization:

Benzhydryl Piperazine (Z): Benzhydrol (53.36g, 0.29 mol) was dissolved in dichloromethane (100 mL). Thionyl chloride (50 mL, 0.69 mol) was added to the reaction mixture, and the reaction mixture was stirred at 40°C for 3 h. The solvent was evaporated under a vacuum and the residue was dissolved in acetonitrile (20 mL). The yield was 90%. Benzhydryl chloride (58.58g, 0.29mol,) was taken in a RBF and piperazine (1.44g, 0.29 mol) was added drop-wise. The reaction mixture was then refluxed for 12 h. The solvent was evaporated under a vacuum, and the residue was dissolved in 250 mL ethyl acetate, washed with 100 mL water, and then treated with 1N HCl (100 mL). Ethyl acetate (3×60 mL) was used to wash the acid phase. The ethyl acetate layer was removed, and the remaining aqueous layer was neutralized with 3N NaOH solutions to achieve a pH of > 10. Then dichloromethane (3×80 mL) was used to extract the aqueous solution. The combined dichloromethane was washed successively with brine, dried over Na_2SO_4, and evaporated under vacuum to receive final compound as solid. The yield was 80% andm. p. was 93°C. The solvent system used for TLC was used n-hexane: ethyl acetate (5: 5).[11]

^{1}H NMR (300 Hz in $CDCl_3$): δ, 7.13-7.42 (m, 10H, Ar-H), 4.20 (s, 1H, -CH of benzhydryl moiety), 2.85 (t, 3H, $-CH_2$ of piperazine), 2.34 (t, 4H, $-CH_2$ of piperazine).

Elemental analysis: Found: C, 80.23; H, 7.19; N, 11.33 $C_{29}H_{32}N_4O$, Requires: C, 80.91; H, 7.99; N, 11.10**.**

1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (5y) [12, 13]: A solution of benzhydryl piperazine (2.52g, 10 mmol,) in dioxane (15 mL) was taken and heat for 10 minutes, then after cooled to 0-5°C in an ice bath. Then 3-Chloro propionyl chloride (13mmol, 1.25 mL) was added with stirring. The reaction mixture was allowed to be stirred at room temperature for 4-6 h. The solvent was removed under a vacuum. The residue was dissolved in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution and finally washed with water. The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure. The yield of the pure compound was (80%), and m.p. was 135°C. The solvent system for TLC was used methanol: ethyl acetate (3: 7).

IR (ATR): 3026 (C-H_{str} (Ar), 2974 (C-H_{str} (aliph), 1705 (C=O), 1643 (C=C $_{str}$(Ar), 1520 (C-C $_{str}$(Ar), 1087 (C-N<) , 785 (-Cl), 671 (C-H_{def}).

^{1}H NMR (300 Hz, $CDCl_3$): δ ,7.17-7.44 (m, 10H, Ar-H), 5.26 (s, 1H, -of CH of benzhydryl moiety) , 3.75 (t, 2H, $-CH_2$ at β position of CH_2), 3.67 (t, 4H, $-CH_2$ of pip), 2.77 (t, 2H, $-CH_2$ at α position) 2.22 (t, 4H, $-CH_2$ of piperazine).

1 - (4 - benzhydryl piperazin – 1 - yl) – 2 - chloro ethanone (3): A solution of benzhydryl piperazine (1.96 g, 15.8 mmol,) in dry dichloromethane was taken and cooled to 0-5°C in an ice bath. TEA (3.30 mL, 23.8 mmol) was added to the cooled reaction mixture and stirred for 10 min, and then chloro acetyl chloride (1.38 mL, 17.4 mmol) was added. The reaction mixture was allowed to be stirred at room temperature for 4-6 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. Firstly, the organic layer was washed with 10 % ammonium chloride Solution, then with distilled water three times approximately and dried with anhydrous sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (85%), mp-121°C. Solvent system for TLC was used methanol: DCM (3: 7) [14, 15].

1-(4-benzhydrylpiperazin-1-yl)-4-chlorobutan-1-one (4): For the synthesis of compound (4) procedure was the same as for compound (5). Only Chloro propionyl chloride was replaced by Chlorobutanoyl chloride. The yield of pure compound was (70%), mp 149°C. methanol: ethyl

acetate (8: 2) was used as mobile phase for TLC experiment.

1-benzhydryl-4-(3-chloropropyl) piperazine (k): To a solution of benzhydryl piperazine (3g, 3.96 mmol,) in acetone (50 mL) and 45 mL of 25% aqueous sodium hydroxide solution was added and stirred for 10 minutes. The spacer or linker 1-bromo-3-chloro propane,(1.23 mL, 3.96 mmol) was added to the reaction mixture and further stirred for a certain time (20 h approximately) at 25°C.Water was added to the mixture and 25 mL of diethyl ether dried over sodium sulphate, filtered, concentrated & purified by column (acetone/ heptane) (6:4) give as yellow syrup. For the synthesis of intermediate (6) procedures was same as for intermediate compound (k). Only 1-bromo-3-chloro propane was replaced with 1-bromo-2-chloro ethane [16, 17].

MS (ESI+) 329 (M^++1), (M^++3) = 331

***N* - (2 - (1*H* – indol – 3 - yl) ethyl) – 2 - (4-benzhydrylpiperazin-1-yl) acetamide (7a):** A suspension of N-(2-(1*H*-indol-3-yl) ethyl)-2-chloroacetamide (0.236 g, 0.001mol), benzhydryl piperazine (0.252g, 0.001mol) and K_2CO_3 (0.414 g, 0.003mol) in dry DMF (10 mL) was stirred at 60°C for 3 h. The reaction mixture was quenched with water (100 ml) and extracted with ethyl acetate (3×50mL). Organic phases were combined, washed with brine, and dried. The solvent was removed under a vacuum. The compound was purified by column chromatography. mp 230°C. The solvent system for TLC was used methanol: DCM (3: 7), yield- 53% [18].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H,-CONH), 6.84-7.29 (m, 10H, Ar-H), 7.11-7.49 (m, 4H, indole), 5.17 (s, 1H,-CH of benzhydryl moiety), 3.51 (s, 2H , -CH_2 at α position of C=O), 3.49 (t, 2H , *J*= 6.4 Hz , -CH_2 at α position of –NH), 2.82 (t, 2H, -CH_2 at β position of –NH), 2.37 (s , 8H , -CH_2 of piperazine).

Found: C, 76.93; H, 7.19; N, 12.33 $C_{29}H_{32}N_4O$, Requires: C, 76.96; H, 7.13; N, 12.38**.**

***N* - (2 - (1*H* – indol - 3 - yl) ethyl) – 3 - (4 –benzhydrylpiperazin-1-yl) propan-1-amine (7c):** Compound (7c) was prepared by the refluxing of 1-benzhydryl-4-(3-chloropropyl) piperazine (0.328g, 0.001 mol), tryptamine (0.48g, 0.003 mol), K_2CO_3 (0.414g, 0.003mol) in dichloromethane (10 mL). The yield of pure compound was (57%), mp-215°C. Solvent system for TLC was used n-hexane: ethyl acetate (8: 2) [18].

^{1}HNMR: (400 MHz, $CDCl_3$) : δ, 8.51 (s, 1H, -NH of indole), 6.92-7.49 (m, 14H, Ar-H), 5.19 (s, 1H, -CH of benzhydryl moiety), 2.90 (t, 2H, *J*= 3.2 Hz -CH_2at α position of –NH), 2.82 (t,2H, *J*= 6.8 Hz -CH_2 at β of –NH), 2.62 (t, 2H, *J*= 6.4 Hz, -CH_2 at γ of piperazine), 2.25 (s, 8H, piperazine), 1.60 (m, 2H, -CH_2 at β position of piperazine),Found: C, 77.57; H, 8.06; N, 12.35 $C_{30}H_{36}N_4$, Requires: C, 79.61; H, 8.02; N, 12.38.

2-(4-benzhydrylpiperazin-1-yl)-*N*-(quinolin-8-yl) acetamide (7d): -Prepared by adopting the same procedure asfor compound (7a). In this 2-chloro-*N*-(quinolin-8-yl) acetamide (0.220g, 0.001mol) was taken as a starting material. mp 198°C. A solvent system for TLC was used n-hexane: ethyl acetate (8: 2). R_f value 0.56. The yield of the pure compound was (61%) [16].

^{1}H NMR(300 MHz, $CDCl_3$): δ11.43 (s, 1H, NH of quinoline) ,7.24-8.79 (m, 16H, Ar-H), 5.19 (s, 1H, -CH of benzhydryl moiety), 3.31 (s, 2H, -CH_2 at α position of pip), 2.36 (s, 8H, piperazine), Found: C, 77.00; H, 6.53; N, 12.80 $C_{28}H_{28}N_4$, Requires: C, 77.04; H, 6.46; N, 12.83.

1 - (4 – benzhydrylpiperazin – 1 - yl) – 2 - (2, 3-dihydro - 1*H* – inden – 5 - ylamino) ethanone (7f):- Compound (7f) was prepared by adopting the same procedure asfor compound 7g, starting from 1-(4-benzhydrylpiperazin – 1 - yl) - 2 –chloro-ethanone, (0.328g, 0.001mol) 5-aminoIndan (0.399g, 0.003 mol) and Sod. carbonate (0.318g, 0.001 mol) in dry ethanol (10 mL). The yield of pure compound was (35%), mp 254°C. R_f value was 0.42. Solvent system for TLC was used n-hexane: ethyl acetate (5: 5) [17].

Found: C, 79.05; H, 7.38; N, 9.84. $C_{28}H_{31}N_3$, Requires: C, 79.02; H, 7.34; N, 9.87

***N*-(2-(4-benzhydrylpiperazin-1-yl) ethyl)-2, 3-dihydro-1*H*-inden-5-amine (7g):** A mixture of1-benzhydryl-4-(2-chloroethyl) piperazine (0.314g, 0.001mol), 5-amino-indan (0.399g, 0.003 mol) and sodium carbonate (0.318g, 0.001 mol) in dry

ethanol (10mL) was refluxed under stirring for 7 h. The reaction mixture was filtered and the organic phase was evaporated under reduced pressure, mp 202°C. A solvent system for TLC was used n-hexane: ethyl acetate (6: 4), R_f value was 0.62. The yield of the pure compound was (51%). [17]

Found: C, 81.68; H, 8.04; N, 10.24 $C_{28}H_{33}N_3$, Requires: C, 81.71; H, 8.08; N, 10.21.

2 - (2 - (1*H* – indol - 3 -yl) ethylamino) – 1 - (4 - benzhydrylpiperazin-1-yl) ethanone (7h): Compound (7h) was prepared by the refluxing of 1-(4 – benzhydrylpiperazin – 1 - yl) – 2 –chloro-ethanone, (0.328g, 0.001mol), tryptamine (0.48gm, 0.003 mol), K_2CO_3 (0.414g, 0.003 mol) in dichloromethane (10 mL). The yield of the pure compound was (36%), mp 187°C. A solvent system for TLC was used n-hexane: ethyl acetate (8: 2). R_f value was 0.74 [18].

^{1}H NMR:-(300 MHz, $CDCl_3$): δ ,10.84 (s, 1H,-NH of indole) δ,6.96-7.49 (m, 14H, Ar-H), 5.10 (s,1H, -CH of benzhydryl moiety), 3.58 (t, 4H, -CH_2), 3.32 (t, 2H, *J*=12.9Hz ,-CH_2 at α position – NH), 3.22 (t, 2H, *J*=5.8 Hz, -CH_2 at β position of – NH), 3.19 (s, 2H, -CH_2 between the C=O (CH_2) - NH), 3.15 (t, 4H, -CH_2).Found: C, 76.93; H, 7.12; N, 12.36 $C_{29}H_{32}N_4$, Requires: C, 76.96; H, 7.13; N, 12.38**.**

3-(2-(1*H* – indol – 3 - yl) ethylamino) – 1 - (4 - benzhydrylpiperazin-1-yl) propan-1-one (7i): Compound (7i) was prepared by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001mol), tryptamine (0.48g, 0.003 mol), K_2CO_3 (0.414g, 0.003mol) in dichloromethane (10 mL). The yield of pure compound was (75%), mp-205 °C. $R_f$value was 0.63. Solvent system for TLC was used n-hexane: ethyl acetate (8: 2) [18].

CONCLUSION: All the synthesized compounds showed significant anticonvulsant activity, except *N*-(2-(1*H*-indol-3-yl) ethyl)- 2 - (4 - benzhydryl piperazin-1-yl) acetamide (7a). Compound like 2-(2 - (1*H* - indol – 3 - yl) ethylamino)-1-(4-benzhydrylpiperazin-1-yl) ethanone (7h), 3-(2-(1*H*-indol-3-yl) ethyl amino)-1-(4-benzhydryl piperazin -1-yl) propan-1-one (7i), were found to show very poor activity. Compound like 1-(4-benzhydrylpiperazin-1-yl)-2-(2, 3-dihydro-1*H*-inden-5-ylamino) ethanone (7f) showed good activity. Compounds like 7d, 7c, and 7g showed excellent anticonvulsant activity and less neurotoxicity, although lower than the reference compound, Phenytoin. Compounds 7a, 7c, 7f, and 7l produce more neurotoxicity and have less protection against convulsive stimuli than the other compounds.

ACKNOWLEDGMENT: Authors are thankful to the Dean & Head, faculty of pharmacy, Integral University, Lucknow, for providing the necessary facilities for the work. The authors are also thankful to Central Drug Research Institute (SAIF), Lucknow, for providing spectral analysis. The manuscript number obtained by the Integral University is IU/R&D/2017-MCN00016.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest regarding the publication of this paper.

REFERENCES:

1. Scheurer ML and Pedley TA: The evaluation and treatment of seizures. New England Journal of Medicine 1990; 323: 1468-1474.
2. Loscher W: New visions in the pharmacology of anticonvulsion. European Journal of Pharmacology 1998; 342: 1-13.
3. Foreman MM, Hanania T, Stratton SC, Wilcox KS: *In-vivo* pharmacological effects of JZP-4, a novel anticonvulsant, in models for anticonvulsant, antimania and antidepressant activity. Pharmacology Biochemistry and Behaviour 2008; 89: 523–534.
4. Kucukguzel I, Kucukguzel SG and Rollas S: Synthesis of some 3-(Arylalkylthio)-4-alkyl/aryl- 5-(4-aminophenyl)-4H-1, 2, 4-triazole derivatives and their anticonvulsant activity. IIFarmaco 2004; 59: 893–901.
5. Narayana B, Raj KKV and Ashalatha BV: Synthesis of some new substituted triazolo [4, 3-a] [1, 4] benzodiazepine derivatives as potent anticonvulsants. European J of Medicinal Chemistry 2006; 41: 417–422.
6. Novack GD, Stark LG and Peterson SL: Anticonvulsant effects of benzhydryl piperazines on Pentylenetetrazol-induced seizures in mice. Neuropharmacology 1978; 17: 633-659.
7. Shakya AK, Kamal M, Balaramnavar VM, Bardaweel SK, Naik RR, Saxena AK and Siddiqui HH: Design, synthesis and evaluation of benzofuran-acetamide scaffold as potential anticonvulsant agent. Acta Pharmaceutica 2016; 66: 353-372.
8. Choi D, Stables JP and Kohn H: Synthesis and anticonvulsant activities of N-Benzyl-2-acetamido-propionamide derivatives. Journal of Medicinal Chemistry 1996; 39: 1907–1916.
9. Pandeya SN, Raja AS and Stables JP: Synthesis of isatinsemicarbazones as potential anticonvulsants – Role of hydrogen bonding. Journal of Pharmacy and Pharmaceutical Sciences 2002; 5: 275-280.
10. Raja AS, Pandeya SN, Panda SS and Stables JP: Synthesis anticonvulsant and antidepressant evaluation of

semicarbazones of acetophenone Mannich bases. Pharmaceutical Chemistry Journal 2007; 41: 302-307.
11. Meng T, Wang J, Peng H and Fang G: Discovery of benzhydryl piperazine derivatives as CB1 receptor inverse agonist *via* privileged structure-based approach. European Journal of Medicinal Chemistry 2010; 45: 1133-1139.
12. Bolognesi ML, Cavalli A, Andrisano V and Bartolini M: Design, synthesis and biological evaluation of ambenonium derivatives as AChE inhibitors. II Farmaco 2003; 58: 917-928.
13. IriepaI, Madrid AI, Galvez E and Bellanato J: Synthesis, structural and conformational study of some amides derived from N-methylpiperazine. Journal of Molecular Structure 2006; 787: 8–13.
14. Gan LL, Fang B and Zhou CH: Synthesis of Azole-containing Piperazine derivatives and Evaluation of their Antibacterial, Antifungal and Cytotoxic Activities. Bulletin of the Korean Chemical Society 2010; 31: 12.
15. Kumar CSA, Prasad SBB, Vinaya K, Chandrappa S, and Thimmegowda NR: Synthesis and *in-vitro* antiproliferative activity of novel 1- benzhydrylpiperazine derivatives against human cancer cell lines. European Journal of Medicinal Chemistry 2009; 44: 1223–1229.
16. Betti L, Zanelli M, Giannaccini G and Manetti F: Synthesis of new piperazine pyridazinone derivatives and their binding affinity toward α_1-, α_2-adrenergic and 5-HT_{1A} serotoninergic receptors. Bioorganic Medicinal Chemistry 2006; 14: 2828–2836.
17. Barbaro R and Betti L: Synthesis and biological activity of new 1, 4-Benzodioxane-aryl piperazine derivative. Bioorganic Medicinal Chemistry 2002; 10: 361-369.
18. Arazany Z, Czarnocki Z, Wojtasiewicz K and Maurin JK: Enantioselective synthesis of (1R)-1-(hydroxymethyl)-2-acetyl-1, 2, 3, 4-tetrahydro-b-carboline from l-(+)-tartaric acid. Tetrahedron: Asymmetry 2002; 11: 2793-2800.

How to cite this article:
Singh K, Shakya AK, Alok S, Naik RR and Kumar A: Synthesis and anti-convulsant activity of novel benzhydryl piperazine derivatives. Int J Pharm Sci & Res 2022; 13(4): 1777-84. doi: 10.13040/IJPSR.0975-8232.13(4).1777-84.