Synthesis and Bio-Evaluations of Some Novel 1,5-Benzodiazepines

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Received: July 20, 2018 Accepted: October 01, 2018

ABSTRACT *A series of 1,5-benzodiazepine derivatives were synthesized by the condensation of o-phenylenediamine and α-chloroacetophenone using cadmium nitrate as catalyst. The newly synthesized compounds were characterized by IR, [1]HNMR and Mass spectra. All the compounds were evaluated for aniinflammatry, antibacterial & antifungal activity. The tested compounds show inhibition ranging from 12% to 49% at 100mg/kg body wt. & 0.06% to 77% at 200mg/kg body wt after 2 hours. Compounds 3j & 3k displayed good antibacterial activity and compounds 3b, 3c, 3d & 3l shows good antibacterial & antifungal activity.*

Keywords: *1,5-benzodiazepine; α-chloroacetophenone; cadmium nitrate.*

1. Introduction:

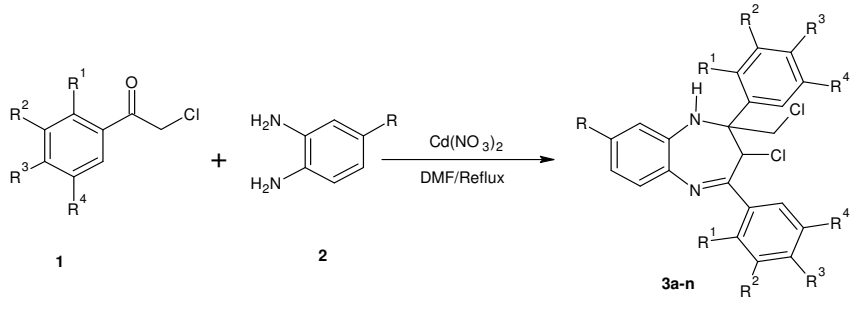
Benzodiazepines are the important compounds having various pharmacological properties. The first use of benzodiazepine as drug was described by Sternbach in 1971.[1] It is a core structure of many drugs. These compounds are widely used as anticonvulsant,[2] antidepressive,[3] antianxiety,[4] tranquilizer,[5] antihypertensive,[6] coronary vasodilatory,[7] antitumor,[8] antimicrobial,[9] antiinflammatory.[10] The research in this field is mainly focused towards synthesis of more pharmacologically active compounds. Generally 1,5-benzodiazepines are synthesized by the condensation of *o*-phenylenediamines with α, β-unsaturated carbonyl compounds,[11] β-haloketones, or ketones.[12] Many catalyst for these condensation are developed as $MgO/POCl_3$,[13] AcOH/MW,[14] SO_4^{--}/ZrO_2,[15] Ionic liquids,[16] $Sc(OTf)_3$,[17] Al_2O_3(acidic)/P_2O_5,[18] Abberlyst-15/[bmim]PF_6[19] $CeCl_3$/NaI supported on SiO_2.[20] However these methods have one or other drawbacks like harsh reaction conditions, sever side reactions, longer reaction time, low yield etc.

Gone through above literature herein is reported the synthesis of some new 1,5-benzodaizepine derivatives by the condensation of *o*-phenylenediamine & α-chloroacetophenone in presence of $Cd(NO_3)_2$. All the products were characterized by spectral data and evaluated for antimicrobial and anti-inflammatory activity.

2. Result and discussion:

2.1 Chemistry:

Different substituted 1,5-benzodiazepines were prepared by the reaction of *o*-phenylenediamines and α-chloroacetophenone in presence of $Cd(NO_3)_2$ (Scheme 1). These compounds were characterized by melting point and IR, [1]HNMR & Mass spectral data. The IR spectra shows a characteristic absorption band at 3250 cm^{-1} for –NH group and 1576 cm^{-1} for –C=N str. The [1]HNMR spectra signals at δ 0.877 (s, 1H) indicates protons on diazepine ring, the signal at δ 9.23 (s, 1H) indicate the proton on nitrogen of diazepine ring and the signals at δ 7.5-8.5 represents aromatic protons. Hence the formation of 1,5-benzodiazepine was confirmed. The mass spectra have given distinct molecular ion peak in accordance with molecular formula.



Scheme 1

Entry	R	R^1	R^2	R^3	R^4	Time (hrs)	Yield (%)
3a	H	H	H	Cl	H	4	71
3b	H	H	I	CL	H	4	72
3c	H	OH	CH_3	H	I	3.5	82
3d	H	OH	I	H	CH_3	3.5	85
3e	H	OH	I	CH_3	I	3.5	80
3f	H	Cl	I	CL	H	4	75
3g	H	H	I	Br	H	4	73
3h	CH_3	H	H	Cl	H	4	74
3i	CH_3	H	I	Cl	H	4	70
3j	CH_3	OH	CH_3	H	I	3.5	83
3k	CH_3	OH	I	H	CH_3	3.5	85
3l	CH_3	OH	I	CH_3	I	3.5	86
3m	CH_3	Cl	I	Cl	H	4	79
3n	CH_3	H	I	Br	H	4	75

2.2 Pharmacology:

All these compounds were screened for *in vivo* anti-inflammatory activity using carrageenan-induced rat hid paw edema method. The value of paw edema is expressed as Mean ± SEM of seven observations and ANOVA followed by post hoc test. Dunnet test was used to compare the groups. Evaluation of anti-inflammatory activity is done by measuring the percent reduction in paw volume, considering the 100% volume at 30 minutes after carrageenan injection in respective groups (Table 1).

$$\%\ Reduction\ in\ paw\ volume = \frac{\text{Vol of paw at 30 minutes interval} - \text{Vol.of paw at subsequent interval}}{\text{Vol of paw at 30 minutes interval!}}$$

All the compounds were shown moderate to good anti-inflammatory activity at 100mg/kg body wt. as well as at 200mg/kg body wt. dose. The tested compounds show inhibition ranging from 12% to 49% at 100mg/kg body wt. & 0.06% to 77% at 200mg/kg body wt after 2 hours.

2.3 Antimicrobial activity:

The in vitro antimicrobial activity of 1,5-benzodiazepine were assessed against two gram positive bacteria *Staphylococcus aureus* & *Bacillus Subtilis,* two gram negative bacteria *Escherichia coli & Salmonell typhi* and antifungal activity against *Penicillium chrysogenum, Fusarium moneliforme, Aspergillus flavus & Aspergillus niger* (Table 2). Compounds 3j & 3k displayed good antibacterial activity and compounds 3b, 3c, 3d & 3l shows good antibacterial & antifungal activity. It was clear that compounds having hydroxyl and iodide substituents show good antimicrobial activities.

3. Conclusion:

Novel 1,5-benzodiazepine derivatives were synthesized from o-phenylenediamine and α-chloroacetophenone using cadmium nitrate as catalyst. The newly synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectra. All the compounds were evaluated for anti-inflammatory, antibacterial & antifungal activity. All the compounds were shown moderate to good anti-inflammatory activity at 100mg/kg body wt. as well as at 200mg/kg body wt. dose. The tested compounds show inhibition ranging from 12% to 49% at 100mg/kg body wt. & 0.06% to 77% at 200mg/kg body wt. Compounds 3j & 3k displayed good antibacterial activity and compounds 3b, 3c, 3d & 3l shows good antibacterial & antifungal activity.

Table 1. Anti-inflammatory activity of 1,5-benzodiazepines

	Dose (mg/kg)	**30 Min.**	**60 Min.**	**2 Hr.**	**3 Hr.**	**5 Hr.**
Control		1.25±0.26	1.28±0.09 (02.4%)	1.42±0.09 (13.6%)	1.62±0.16 (29.60%)	1.77±0.15 (41.60%)
3a	100	1.39±0.35	1.59±0.21 (14.13)	1.63±016 (17.26%)	1.53±0.56 (10.07%)	1.43±13 (02.87%)
	200	1.36±0.10	1.44±0.30 (05.88%)	1.49±0.12 (9.55%)	1.47±0.31 (08.08%)	1.41±0.21 (03.67%)
3b	100	1.40±0.35	1.85±0.44 (32.14%)	2.09±0.48 (49.28%)	2.04±0.48 (45.71%)	1.77±0.42 (26.42%)
	200	1.31±0.32	1.82±0.31	2.31±0.32	2.18±0.37	1.6±0.18

			(38.93%)	(77.69%)	(66.41%)	(22.13%)
3c	100	1.46±0.38	1.87±0.38 (28.08%)	2.13±0.39 (45.89%)	2.02±0.37 (38.35%)	1.87±0.22 (28.08%)
	200	1.50±0.10	1.60±0.09 (06.66%)	1.71±0.18 (14.00%)	1.66±0.10 (10.66%)	1.56±0.09 (4.00%)
3d	100	1.49±0.31	168±0.17 (12.75%)	1.82±0.13 (12.14%)	1.75±0.16 (17.44%)	1.58±0.21 (06.04%)
	200	1.16±0.21	1.30±0.30 (12.06%)	1.38±0.35 (18.96%)	1.28±0.23 (10.34%)	1.23±0.15 (6.03%)
3e	100	1.24±0.30	1.38±0.25 (11.29%)	1.50±0.29 (20.96%)	1.34±0.34 (08.06%)	1.30±0.13 (04.83%)
	200	1.51±0.12	1.54±0.21 (1.98%)	1.64±0.21 (08.60%)	1.71±0.12 (13.24%)	1.68±0.31 (11.25%)
3f	100	1.49±0.07	1.69±0.32 (13.42%)	1.86±0.21 (24.83%)	1.84±0.14 (23.48%)	1.73±0.15 (16.10%)
	200	1.56±0.12	1.71±0.31 (9.61%)	1.75±0.31 (12.17%)	1.80±0.14 (15.38%)	1.72±0.31 (10.25%)
3g	100	1.39±0.17	1.59±0.19 (14.38%)	1.66±0.23 (19.42%)	1.73±0.23 (24.46%)	1.70±0.23 (22.30%)
	200	1.35±0.41	1.39±0.51 (2.96%)	1.43±0.32 (5.92%)	1.52±0.34 (12.59%)	1.42±0.12 (5.18%)
3h	100	1.57±0.31	1.62±0.23 (3.18%)	1.80±0.13 (14.19%)	1.73±0.21 (10.19%)	1.69±0.36 (07.63%)
	200	1.57±0.15	1.58±0.16 (0.06%)	1.63±0.21 (03.82%)	1.71±0.16 (08.90%)	1.61±0.31 (2.50%)
3i	100	1.24±0.19	1.50±0.19 (21.90%)	1.59±0.54 (28.22%)	1.53±0.51 (23.38%)	1.43±0.32 (15.32%)
	200	1.40±0.16	1.61±0.15 (15.00%)	1.70±0.21 (21.42%)	1.68±0.16 (20.00%)	1.62±0.21 (15.71%)
3j	100	1.32±0.32	1.51±0.21 (14.39%)	1.53±0.25 (15.90%)	1.43±0.12 (08.33%)	1.41±0.23 (06.81%)
	200	1.37±0.31	1.39±0.15 (01.45%)	1.52±0.14 (10.9%)	1.43±0.18 (4.37%)	1.45±0.21 (05.80%)
3k	100	1.4±0.69	1.48±0.25 (5.71%)	1.52±0.35 (08.57%)	1.50±0.14 (7.14%)	1.47±0.48 (05.00%)
	200	1.41±0.17	1.47±0.19 (04.20%)	1.59±0.48 (12.70%)	1.53±0.34 (08.51%)	1.52±0.19 (07.80%)
3l	100	1.35±0.37	1.75±0.58 (29.62%)	1.79±0.36 (32.59%)	1.72±0.36 (27.40%)	1.65±0.28 (22.22%)
	200	1.43±0.18	1.52±0.37 (06.29%)	1.61±0.16 (12.58%)	1.56±0.14 (09.09%)	1.51±0.31 (05.59%)
3m	100	1.53±0.35	1.73±0.34 (13.07%)	1.98±0.34 (29.41%)	1.78±0.24 (16.33%)	1.69±0.43 (06.53%)
	200	1.42±0.14	1.57±0.37 (10.56%)	1.78±0.21 (25.35%)	1.68±0.34 (18.30%)	1.63±0.51 (14.78%)
3n	100	1.21±0.12	1.36±0.21 (12.39%)	1.42±0.54 (17.35%)	1.41±0.54 (16.52%)	1.39±0.123 (14.87%)
	200	1.53±0.31	1.72±0.25 (12.41%)	1.78±0.34 (16.33%)	1.75±0.61 (12.41%)	1.68±0.14 (09.80%)
Diclofenac		1.35±0.317	1.64±0.32 (93.71%)	2.09±0.2 (19.42%)	1.92±0.096 (09.71%)	1.8±0.34 (02.85%)

Table 2. Antibacterial & Antifungal activity of 1,5-benzodiazepines

Antibacterial activity						Antifungal activity				
Comp.	E. Coli	S. Typhi	S. Aureus	B. Subtilis		Comp	P. Chrysogenum	F. Moneliforme	A. Flavus	A. Niger
3a	11	3a	25	20		3a	-ve	-ve	ve	-ve
3b	12	3b	27	25		3b	-ve	-ve	-ve	-ve
3c	16	3c	35	31		3c	-ve	-ve	-ve	-ve
3d	15	3d	32	30		3d	-ve	-ve	-ve	-ve
3e	14	3e	30	31		3e	-ve	-ve	-ve	-ve

3f	11	3f	22	25		3f	-ve	-ve	-ve	-ve
3g	-	3g	16	18		3g	-ve	-ve	-ve	-ve
3h	11	3h	21	18		3h	-ve	-ve	RG	RG
3i	11	3i	19	17		3i	-ve	-ve	-ve	-ve
3j	13	3j	29	28		3j	-ve	-ve	RG	RG
3k	11	3k	27	29		3k	-ve	-ve	RG	RG
3l	12	3l	23	28		3l	-ve	-ve	-ve	-ve
3m	--	3m	28	30		3m	-ve	-ve	-ve	-ve
3n	--	3n	22	25		3n	-ve	-ve	-ve	-ve
DMSO	-	DMSO	-	-		DMSO	+ve	+ve	+ve	+ve
Penicillin	14	14	34	22		Griseofulvin	-ve	-ve		ve

Legends- + ve – Growth; -ve - No Growth; RG – Reduced Growth

4. Experimental:

4.1 General:

All melting points were determined by open capillary and are uncorrected. IR spectra were scanned on 'Schimadzu' FT-IR spectrometer using KBr pallet, ^{1}HNMR were recorded on 'Avance-300' in $CDCl_3$ and TMS as internal standard. Mass spectra were recorded in Electron Impact mode. The purity of compounds was checked by TLC using ethyl acetate: pet ether (3:7) as eluent.

4.2 Antimicrobial activity:

The agar cup method[21] was employed to measure antibacterial activity. Sterile agar was seeded with turbid suspension of selected bacteria and poured in sterile Petri dish. Cups of 10 mm diameter were made with sterile cork borer 100µl solution of test compound in DMSO was added in the cup under septic condition. DMSO was used as negative control and Penicillin as positive control. The plates are incubated at 37^{o}C for 24 hours. Zone of inhibition were recorded in millimeters using zone reader.

4.3 Antifungal activity:

Antifungal activity was studied by Poison Plate Method.[22] Sterile Potato Dextrose Agar was used as medium. The test samples were added to the sterile medium so as to get final concentration as 1%. DMSO was used as negative control & Gresiofulvin as positive control. The fungal suspension was spot inoculated on the plates prepared using compounds with the help of nicrome wire loop. The plates were incubated at room temperature for 48 hours.

Incubated plates were observed for the growth of inoculated fungi. Results were noted as growth of fungi (no antifungal activity), reduced growth of fungi (moderate antifungal activity) & no growth of fungi (antifungal activity).

4.4 Pharmacology:

Anti-inflammatory activity was performed by carrageenan induced paw edema method in rats[23] using Diclofenac as standard. The experiments were carried out by strictly following rule and regulations of Institutional Animal Ethics Committee (Animal Ethics Committee AISSMS College of Pharmacy, Pune). Edema was induced by sub-plantar injection of 0.1ml of freshly prepared 1% carrageenan into the right hind paw of the male Wistar rats (100g-150g). The animals were starved 12 hours before experiment. The test compounds were given orally as a suspension in 1% carboxyl methyl cellulose 30 min. prior to carrageenan injection.

The animals were divided into 30 groups (n=3).

Group 1- served as control and received carrageenan (1% W/V in saline).

Group 2- served as standard and received Diclofenac sodium (25 mg/kg p.o)

Group 3 to 30 - received the test compounds (100 and 200 mg/kg p.o) respectively.

The volume of paw edema was measured at 30, 60, 2 hr, 3 hr & 5 hr. after above treatments using plethysmograph. The values for edema volume are as mean ± SEM of seven observations and ANOVA followed by post hoc test. Dunnet test was used to compare the groups.

4.5 General procedure for the preparation of 1, 5-benzodiazepines (3a-n):

Mixture of α-chloroacetophenone (2 mmole), *o*-phenylenediamine (1.0 mmole), and cadmium nitrate (10mol %) in DMF (15 mL) was refluxed for a 3-4 hours. The progress of reaction was monitored by TLC using ethyl acetate: pet ether (3:7). After completion of the reaction the solvent was removed by

distillation under reduce pressure. The crude product was recrystllized from ethanol to afford the corresponding 1,5-benzodiazepines.

(Z)-3-chloro-2-(chloromethyl)-2,4-bis(4-chlorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine (3a) Mp. 136 °C; IR (KBr) cm^{-1} 3250 (–NH), 3085 (–CH), 1592 (-C=N), 1538 (–C=C Ar), 667 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.877 (s, 1H), 1.25 (s, 2H) 7.73-7.81 (M, 8H), 8.10-8.16 (m, 4H), 9.3 (s, 1H); M.S. *m/z* 447 M^+; *Anal. % Calcd* for $C_{22}H_{16}Cl_4N_2$ (448.00): C, 58.69; H, 3.58; N, 6.22. Found: C, 68.50; H, 3.62; N, 6.20%.

(Z)-3-chloro-2,4-bis(4-chloro-3-iodophenyl)-2-(chloromethyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine (3b) Mp. 122 °C; IR (KBr) cm^{-1} 3250 (–NH), 3085 (–CH), 1576 (-C=N), 1538 (–C=C Ar), 667 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.867 (s, 1H), 1.25 (s, 2H), 7.70-7.81 (M, 6H), 8.08-8.15 (m, 4H), 9.33 (s, 1H); M.S. *m/z* 701 M^+; *Anal. % Calcd* for $C_{22}H_{14}Cl_4I_2N_2$ (701.79): C, 37.64; H, 2.01; N, 3.99. Found: C, 37.60; H, 2.02; N, 4.08%.

2-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-5-iodo-3-methylphenyl)-1H-benzo[b][1,4] diazepin-2-yl)-4-iodo-6-methylphenol (3c) Mp. 142 °C; IR (KBr) cm^{-1} 3363 (–OH), 3155 (–NH), 3025 (–CH), 1572 (-C=N), 1544 (–C=C Ar), 670 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.967 (s, 1H), 1.25 (s, 2H), 2.32 (s, 6H, 2-CH_3), 7.70(s, 2H, 2Ar-H), 7.81 (s, 2H, 2Ar-H), 8.08-8.15 (m, 4H), 9.13 (s, 1H), 12.13 (s, 2H, 2-OH); M.S. *m/z* 692 M^+; *Anal. % Calcd* for $C_{24}H_{20}Cl_2I_2N_2O_2$ (993.14): C, 41.59; H, 2.91; N, 4.04. Found: C, 40.60; H, 3.00; N, 4.00%.

2-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-3-iodo-5-methylphenyl)-1H-benzo[b][1,4] diazepin-2-yl)-6-iodo-4-methylphenol (3d) Mp. 145 °C; IR (KBr) cm^{-1} 3355 (–OH), 3165 (–NH), 3030 (–CH) 1572 (-C=N), 1554 (–C=C Ar), 6702 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.962 (s, 1H), 1.26 (s, 2H),2.36 (s 6H, 2-CH_3), 7.72(s, 2H, 2-ArH), 7.83 (s, 2H, 2-ArH), 8.08-8.15 (m, 4H), 9.13 (s, 1H), 12.15 (s, 2H, 2-OH); M.S. *m/z* 992 M^+; *Anal. % Calcd* for $C_{24}H_{20}Cl_2I_2N_2O_2$ (993.14): C, 41.59; H, 2.91; N, 4.04. Found: C, 40.62; H, 3.01; N, 4.02%.

6-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-3,5-diiodo-4-methylphenyl)-1H-benzo[b] [1,4]diazepin-2-yl)-2,4-diiodo-3-methylphenol (3e) Mp. 152°C; IR (KBr) cm^{-1} 3364 (–OH), 3153 (–NH), 3026 (–CH) 1575 (-C=N), 1547 (–C=C Ar), 670 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.943 (s, 1H), 1.25 (s, 2H),2.32 (s 6H, 2-CH_3), 7.70(s, 2H, 2 Ar-H), 8.08-8.15 (m, 4H), 9.13 (s, 1H), 12.13 (s, 2H, 2-OH); M.S. *m/z* 943 M^+; *Anal. % Calcd* for $C_{24}H_{18}Cl_2I_4N_2O_2$ (944.93): C, 30.51; H, 1.92; N, 3.39. Found: C, 30.60; H, 2.00; N, 3.39%.

(Z)-3-chloro-2,4-bis(2,4-dichloro-3-iodophenyl)-2-(chloromethyl)-2,3-dihydro-1H-benzo[b][1,4] diazepine (3f) Mp. 115 °C; IR (KBr) cm^{-1} 3363 (–OH), 3155 (–NH), 3025 (–CH), 1572 (-C=N), 1544 (–C=C Ar), 670 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.968 (s, 1H), 1.23 (s, 2H), 7.71- 7.81 (m, 4H), 8.08-8.13 (m, 4H), 9.11 (s, 1H); M.S. *m/z* 769 M^+; *Anal. % Calcd* for $C_{22}H_{12}Cl_6I_2N_2$ (770.89): C, 34.28; H, 1.57; N, 3.63. Found: C, 34.30; H, 1.60; N, 3.70%.

(Z)-2,4-bis(4-bromo-3-iodophenyl)-3-chloro-2-(chloromethyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine (3g) Mp. 135 °C; IR (KBr) cm^{-1} 3257 (–NH), 3059 (–CH), 1582 (-C=N), 1545 (–C=C Ar), 669 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.867 (d, 1H), 1.25 (s, 2H), 7.70-7.81 (M, 6H), 8.08-8.15 (m, 4H), 9.33 (s, 1H); M.S. *m/z* 789 M^+; *Anal. % Calcd* for $C_{22}H_{14}Br_2Cl_2I_2N_2$ (790.88): C, 33.41; H, 1.78; N, 3.54. Found: C, 33.50; H, 1.75; N, 3.59%.

(Z)-3-chloro-2-(chloromethyl)-2,4-bis(4-chlorophenyl)-2,3-dihydro-8-methyl-1H-benzo[b][1,4]diazepine (3h) Mp. 132 °C; IR (KBr) cm^{-1} 3250 (–NH), 3085 (–CH), 1592 (-C=N), 1538 (–C=C Ar), 667 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.877 (s, 1H), 1.25 (s, 2H), 2.33(s, 3H) 7.73-7.81 (M, 8H), 8.10-8.16 (m, 3H), 9.3 (s, 1H); M.S. *m/z* 464 M^+; *Anal. % Calcd* for $C_{23}H_{18}Cl_4N_2$ (464.21): C, 59.51; H, 3.91; N, 6.03. Found: C, 59.50; H, 3.90; N, 6.05%.

(Z)-3-chloro-2,4-bis(4-chloro-3-iodophenyl)-2-(chloromethyl)-2,3-dihydro-8-methyl-1H-benzo[b][1,4] diazepine (3i) Mp. 138 °C; IR (KBr) cm^{-1} 3423 (–NH), 3089 (–CH) 2979 (C-H), 1589 (-C=N), 1530 (–C=C Ar), 657 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.32 (s, 1H), 2.61 (s, 2H), 2.86 (s, 3H), 7.4-8.15 (m, 9H), 9.19 (s, 1H); M.S. *m/z* 715 M^+; *Anal. % Calcd* for $C_{23}H_{16}Cl_4I_2N_2$ (716.00): C, 38.58; H, 2.25; N, 3.91. Found: C, 38.50; H, 2.20; N, 3.90%.

6-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-4-iodo-3-methylphenyl)-8-methyl-1H-benzo [b][1,4]diazepin-2-yl)-3-iodo-2-methylphenol (3j) Mp. 142 °C; IR (KBr) cm^{-1} 3363 (–OH), 3155 (–NH), 3025 (–CH), 1572 (-C=N), 1544 (–C=C Ar), 670 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.967 (d, 1H), 1.25 (s, 2H), 2.32 (s, 6H, 2-CH_3), 2.6 (s, 3H), 7.70(s, 2H, 2 Ar-H), 7.81 (s, 2H, 2 Ar-H), 8.08-8.15 (m, 3H), 9.11 (s, 1H), 12.11 (s, 2H, 2-OH); M.S. m/z 706 M^+; *Anal. % Calcd* for $C_{25}H_{22}Cl_2I_2N_2O_2$ (707.16): C, 42.46; H, 3.14; N, 3.96. Found: C, 42.50; H, 3.12; N, 3.95%.

2-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-3-iodo-5-methylphenyl)-8-methyl-1H-benzo [b][1,4]diazepin-2-yl)-6-iodo-4-methylphenol (3k) Mp. 141 °C; IR (KBr) cm^{-1} 3366 (–OH), 3156 (–NH), 3015 (–CH), 1575 (-C=N), 1545 (–C=C Ar), 671 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.966 (s, 1H), 1.25

(s, 2H), 2.31 (s, 6H, 2-CH_3), 2.62 (s, 3H), 7.71(s, 2H, 2 Ar-H), 7.8 (s, 2H, 2 Ar-H), 8.08-8.15 (m, 3H), 9.12 (s, 1H), 12.13 (s, 2H, 2-OH); M.S. *m/z* 706 M^+; *Anal. % Calcd* for $C_{25}H_{22}Cl_2I_2N_2O_2$ (707.16): C, 42.46; H, 3.14; N, 3.96. Found: C, 42.45; H, 3.15; N, 4.00%.

6-((Z)-3-chloro-2-(chloromethyl)-2,3-dihydro-4-(2-hydroxy-3,5-diiodo-4-methylphenyl)-8-methyl-1H-benzo[b][1,4]diazepin-2-yl)-2,4-diiodo-3-methylphenol (3l) Mp. 150 ^oC; IR (KBr) cm^{-1} 3363 (–OH), 3153 (–NH), 3021 (–CH), 1572 (-C=N), 1544 (–C=C Ar), 670 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.967 (s, 1H), 1.25 (s, 2H),2.32 (s, 6H, 2-CH_3), 2.12 (s, 3H), 7.81 (s, 2H, 2Ar-H), 8.08-8.15 (m, 3H), 9.13 (s, 1H), 12.13 (s, 2H, 2-OH); M.S. *m/z* 957 M^+; *Anal. % Calcd* for $C_{25}H_{20}Cl_2I_4N_2O_2$ (958.96): C, 31.31; H, 2.10; N, 2.92; Found: C, 31.30; H, 2.15; N, 2.98%.

(Z)-3-chloro-2,4-bis(2,4-dichloro-3-iodophenyl)-2-(chloromethyl)-2,3-dihydro-8-methyl-1H-benzo[b][1,4]diazepine (3m) Mp. 125 ^oC; IR (KBr) cm^{-1} 3365 (–OH), 3151 (–NH), 3025 (–CH), 1572 (-C=N), 1548 (–C=C Ar), 671 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.997 (d, 1H), 1.25 (s, 2H), 2.12 (s, 3H), 7.70- 7.81 (m, 4H), 8.08-8.15 (m, 3H), 9.13 (s, 1H),; M.S. *m/z* 783 M^+; *Anal. % Calcd* for $C_{23}H_{14}Cl_6I_2N_2$ (784.87): C, 35.20; H, 1.80; N, 3.57 Found: C, 35.22; H, 1.85; N, 3.55%.

(Z)-2,4-bis(4-bromo-3-iodophenyl)-3-chloro-2-(chloromethyl)-2,3-dihydro-8-methyl-1H-benzo[b][1,4]diazepine (3n) Mp. 129 ^oC; IR (KBr) cm^{-1} 3258 (–NH), 3059 (–CH), 1580 (-C=N), 1545 (–C=C Ar), 669 (–C-Cl); ^{1}HNMR (300 MHz, $CDCl_3$) δ 0.867 (s, 1H), 1.25 (s, 2H), 2.35 (s, 3H), 7.70-7.81 (M, 4H), 8.08-8.15 (m, 3H), 9.3 3 (s, 1H); M.S. *m/z* 803 M^+; *Anal. % Calcd* for $C_{23}H_{16}Br_2Cl_2I_2N_2$ (804.90): C, 34.32; H, 2.00; N, 3.48Found: C, 34.35; H, 2.02; N, 3.45%.

5. References:

1. Sternbach L. H. Angew. Chem., Int. Ed. Engl. 10, **1971**, 34-42.
2. Narayana B., Vijaya Raj K. K., Ashalatha, B. V., Suchetha Kumari N. Eur. J. Med. Chem., 41,**2006**, 417-422.
3. Inoue H., Konda M., Hashiyama T., Otsuka H., Takahashi K., Gaino M., Date T., Aoe K., Takeda M., Murata S., Narita H., Nagao T. J. Med. Chem., 34, **1991**, 675-687.
4. Devi T. K., Achaiah G., Reddy V. M. J. Indian Chem. Soc., 65, **1988,** 567-570.
5. Kugita H., Inoue H., Ikezaki M. Jap. Pat. 1971, 46016749, Chem. Abstr., 75, 1971, 63848.
6. Inoue H., Konda M., Hashiyama T., Otsuka H., Takahashi K., Gaino M., Date T., Aoe K., Takeda M., Muruta S., Narita H., Nagao T. J. Med. Chem., 34,. **1991**, 675-687.
7. Kugita H., Takeo S., Matsushima M. Jap. Pat. **1972**, 47008544, Chem. Abstr., 77, 1972, 5556.
8. P. G Baraldi, M. G. Pavani, M. Nunez, P. Brigidi, B. Vitali, R. Gambari and R. Romagnoli Bio Org. Med. Chem., **10**, **2002,** 449-456.
9. Md. Salahuddin, Sanjay Singh, S. M. Shantakumar Rasayan J. Chem., 2(1), **2009**, 167-173.
10. Ishwar Bhat, Abhishek Kumar Asian J. Pharma. Clinical Res., 9(4), **2016**, 63-66.
11. Stahlhofen, P.; Ried, W. Chem. Ber., 90, **1957**, 815-819.
12. Ried, W.; Torinus, E. Chem. Ber,., 92, **1959**, 2902-2909.
13. Balakrishna, M. S.; Kaboudin, B. Tet. Lett., 42, **2001**, 1127-1129.
14. Minothora Pozarentzi, Julia Stephanidou-Stephanatou and Constantinos A. Tsoleridis Tet. Lett., 43, **2002**, 1755–1758.
15. Benjaram M. Reddy and Pavani M. Sreekanth Tet. Lett., 44, **2003**, 4447–4449
16. D. V. Jarikote, S. A. Siddiqui, R. Rajagopal, Thomas Daniel, R. J. Lahoti and K. V. Srinivasan Tet. Lett., 44, **2003**, 1835–1838.
17. Surya K. De and Richard A. Gibbs Tet. Lett., 46, **2005**, 1811–1813.
18. Babak Kaboudin and Kian Navaee heterocycles, 55, (8), 1443 – 1446.
19. J. S. Yadav, B. V. S. Reddy, B. Eshwaraiah and K. Anuradha Green Chemistry, 4, **2002**, 592–594
20. Gowravaram Sabitha, G. S. Kiran Kumar Reddy, K. Bhaskar Reddy,N. Mallikarjuna Reddy, J. S. Yadav Adv. Synth. Catal., 346, **2004**, 921-923.
21. C. H. Collins, Microbiological Methods (Butterworth, London), 1967, 364.
22. Cruikshank R. J., Durgid P., Swain R. R., Medical Microbiology – Vol. 1 (Churchill Livingstone) **1998.**
23. Winter C. A., Risley E. A., Nuss W. G. Proc. Soc. Exp. Biol. Med., 111, **1962,** 544-547.