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Synthesis, Characterization and Antiulcerative Activity of Diazepine Derivatives of Cinitapride

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Several 2,4-disubstituted 2,3-dihydro 1,5-benzodiazepine analogues of cinitapride were prepared *via* cyclocondensation of the corresponding 1,3-diaryl-2-propen-1-ones with cinitapride derivatives in acidic media. Antiulcer activity of all the resulted 1,5-benzo diazepine derivatives were studied in mice.

Key Words: Diazepine, Cinitapride, Antiulcerative, Prokinetic, 1,3-Diaryl-2-propen-1-ones.

INTRODUCTION

4-Amino-N-[1-(3-cyclohexen-1-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide(+)-tartrate (**1a** cinitapride hydrogen tartrate) is a prokinetic benzamide derivative simulating gastrointestinal motility and is a commercially successful antiulcerative active pharmaceutical ingredient[1,2]. Reported general method for the preparation of this compound involved condensation of 4-amino-2-ethoxy-5-nitrobenzoic acid with 4-amino-1-(3-cyclohexen-1-ylmethyl)piperidine in the presence of triethylamine and ethyl chloroformate and subsequent salt formation with L(+)tartaric acid[3]. In continuation of our study of imidazole analogues of cinitapride[4], herein we report the synthesis and antiulcerative activity study of diazapine derivatives of cinitapride. The benzo diazepine is a pharmacophore present in several drugs, such as emedastine (antihistaminic)[5], cloxazolam (anxiolytic)[6], bromazepam (anxiolytic)[7], clobazam (anticonvulsant)[8], clozapine (antipsychotic)[9], dibenzepin (antidepressant)[10] cholecystokinin A and B antagonists[11], opioid receptor ligands[12], platelet-activating factor antagonists[13] and HIV reverse transctriptase inhibitors[14]. In the light of these observations, we are interested to incorporate 1,5-diazepine moiety in the

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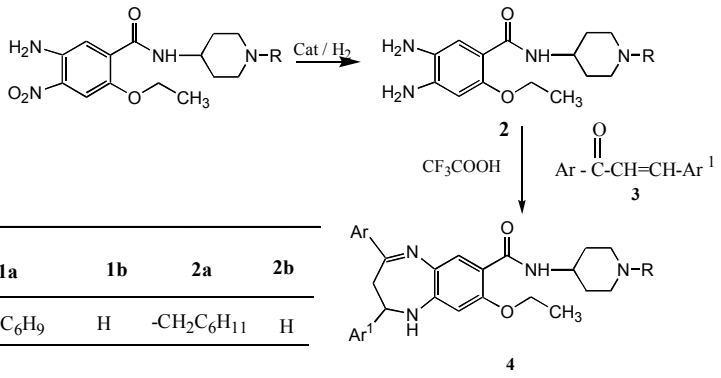
cinitapride skeleton and study their antiulcerative properties. Cyclocondensation of *ortho*-phenylendiamine with a three-carbon source such as ketones[15-17] or chalcones[18,19] is a generally practiced method for the synthesis of 1,5-benzodiazepine derivatives. We adopted a similar strategy in the synthesis of desired compounds.



Compounds	1a	1b	2a	2b
R	$-CH_2C_6H_9$	H	$-CH_2C_6H_{11}$	H

Compound	3a/4a	3b/4b	3c/4c	3d/4d	3e/4e	3f/4f	3g/4g	4h	4i	4j
Ar	H	Br	Br	Cl	Cl	H	H	Br	H	H
Ar^1	H	F	H	F	H	CH_3	F	H	CH_3	H
R	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	$CH_2C_6H_{11}$	H	H	H

Scheme-I

1,2-Diamino derivative **2a** derived[4] from the catalytic hydrogentation of cinitapride derivative **1a** is chosen as the apt precursor. Condensation of **2a** with 1,3-diphenyl-2-propen-1-one **3** in trifluoroacetic acid at ambient temperature followed by usual work up afforded the corresponding diazepine derivative **4a**. Six other chalcones **3b-3g** were reacted with diamine **2a** in a similar manner to get the corresponding diazepine derivatives **4b-4g** in 65-74 % yield. Further structural variation in diamine derivative[4] by using compound **2b** was also examined in the formation of corresponding diazepine derivative **4h-4j**. All the diazepine derivatives are fully characterized based on their IR, ^{1}H NMR, mass spectral data and elemental analysis.

Gastrointestinal activity: Prokinetic studies were conducted in pharmacology Lab., Dr. Reddy's Research Foundation, Hyderabad. Compounds were tested on male swiss albino mice (body weight 20-25 g) at dosage of 210 mg/kg.

Methodology: Adult swiss albino mice of either sex weighing between 20-25 g were used for our study. Mice were fasted for 24 h prior

to experimentation but had free access to water. Phenol red (0.5 mL) meal was administered 1 h. after the drug administration. Animals were sacrificed by cervical dislocation 15 min after the administration of the meal. Abdomen was opened and stomach was dissected out. The stomach was cut into pieces and homogenized with 25 mL of 0.1 N NaOH. To this 1.9 mL of homogenate, 0.19 mL of trichloroaceticacid (20 % w/v) was added and centrifuged at 3000 rpm for 20 min. To 1.5 mL of supernatant, 0.5 mL of 0.5 N NaOH was added and absorbance was measured at 560 nm. This correlates to the concentration of phenol red in the stomach, which in turn depends on gastric emptying (GE).

$$\% \text{ GE} = (1\text{-}X/Y) \times 100$$

where, X = Absorbance of phenol red recovered after 15 min after test meal. Y = Absorbance of phenol red recovered at 0 min following test meal.

Gastric emptying in mice by phenol red assay

Animals: Swis albino mice; **Sex:** Male; **Bodyweight:** 20-30 g (n = 6); **Dose:** 10 mg/kg; **Route of administration:** oral; **Vehicle:** 0.25 % CMC; **Test meal:** Phenol red meal; **Volume administered:** 0.5 mL.

Treatment	Dose/kg	GE (%)	Treatment	Dose/kg	GE (%)
Control	-	65 ± 4	**4e**	10	50 ± 2
4	10	52 ± 7	**4f**	10	62 ± 6
4a	10	48 ± 2	**4g**	10	64 ± 4
4b	10	66 ± 6	**4h**	10	61 ± 6
4c	10	75 ± 1	**4i**	10	59 ± 7
4d	10	62 ± 6	Cinitapride	10	83 ± 1

*p, 0.05; others are not significant.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary. IR spectra were recorded on a Nicolet 550 Series II Maguna FT-IR spectrometer. ^{1}H NMR spectra were measured on Varian Gemini 200 MHz spectrometer in DMSO-d_6 with TMS as the internal standard. Mass spectra were recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS. Micro analyses were performed for C, H, N (Dr. Reddy's Research Foundation, Hyderabad) and were within ± 0.4 % of theoretical values, silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230) mesh.

General procedure for the preparation of 4a-j: To a solution of diamino compound (**2a/2b**, 0.0267 mol) in trifluoro acetic acid (100 mL),

1,3-diaryl-2-propen-1-one (**3a-g**, 0.28 mol) was added and reaction mixture was stirred at room temperature for 8 h, reaction mixture was quenched with water (300 mL) stirred and extracted with ethyl acetate (3 × 150 mL). Organic phase was washed with aqueous sodium bicarbonate solution (2 × 100 mL), concentrated under vacuum and residue was passed through silica column using ethyl acetate and hexane mixtures to provide the corresponding diazepine derivative (**4a-j**) as a crystalline solid.

N-(1-(Cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2,3-dihydro-2,4-diphenyl-1H-benzo[b][1,4] diazepine-7-carboxamide (4a): Yield: 68 %; m.p.: 195-198ºC. IR (KBr, cm^{-1}): 3341 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 11H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 565.5 (M^+).C, H, N Analysis: Calcd. for $C_{36}H_{44}N_4O_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.51; H, 7.81; N, 9.88.

4-(4-Bromophenyl)-N-(1-(cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2-(4-fluorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine-7-carboxamide (4b): Yield 66 % ; m.p. 160-165ºC IR (KBr, cm^{-1}): 3395 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 0.9 (t, 3H, CH), 1.0-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-8.0 (s, 9 H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 661.65 (M^+). C, H, N Analysis: Calcd. for $C_{36}H_{42}N_4O_2BrF$: C, 65.35; H, 6.40; N, 8.47. Found: C, 65.39; H, 6.37; N, 8.41.

4-(4-Bromophenyl)-N-(1-(cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepine-7-carboxamide (4c): Yield 69 % ; m.p. 132-136ºC. IR (KBr, cm^{-1}): 3400 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10 H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 643.5 (M^+). C, H, N Analysis: Calcd. for $C_{36}H_{43}N_4O_2Br$: C, 67.18; H, 6.73; N, 8.70. Found: C, 67.13; H, 6.68; N, 8.73.

(4-(4-Chlorophenyl)-N-(1-(cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2-(4-fluorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine-7-carboxamide (4d): Yield 70 %; m.p. 158-162ºC, IR (KBr, cm^{-1}): 3414 ν(NH), ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 9H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 617.5 (M^+). C, H, N Analysis: Calcd. for $C_{36}H_{42}N_4O_2ClF$: C, 70.06; H, 6.86; N, 9.08. Found: C, 70.01; H, 6.85; N, 9.05.

4-(4-Chlorophenyl)-N-(1-(cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2,3-dihydro-2-phenyl-1H-benzo[b][1,4]diazepine-7-carboxamide (4e): Yield 66 %; m.p. 126-130ºC: IR (KBr, cm^{-1}): 3395 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 599.6 (M^+). C, H, N Analysis: Calcd. for $C_{36}H_{43}N_4O_2Cl$: C, 72.16; H, 7.23; N, 9.35. Found: C, 72.14; H, 7.20; N, 9.30.

N-(1-(Cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2,3-dihydro-4-phenyl-2-p-tolyl-1H-benzo [b][1,4]diazepine-7-carboxamide (4f): Yield 71 % ; m.p. 205-211ºC. IR (KBr, cm^{-1}): 3395 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.1 (s, 3H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 579.3 (M^+). C, H, N Analysis: Calcd. for $C_{37}H_{46}N_4O_2$: C, 76.78; H, 8.01; N, 9.68. Found: C, 76.72; H, 8.00; N, 9.63.

N-(1-(Cyclohexylmethyl)piperidin-4-yl)-8-ethoxy-2-(4-fluorophenyl)-2,3-dihydro-4-phenyl-1H-benzo[b][1,4]diazepine-7-carboxamide (4g): Yield 72 %; m.p. 140-146ºC. IR (KBr, cm^{-1}): 3395 ν(NH). ^{s}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.1-1.2 (m, 11H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.2 (m, 2H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 583.5 (M^+). C, H, N Analysis: Calcd. for $C_{36}H_{43}N_4O_2F$: C, 74.20; H, 7.44; N, 9.61. Found: C, 74.18; H, 7.40; N, 9.58.

4-(4-Bromophenyl)-8-ethoxy-2,3-dihydro-2-phenyl-N-(piperidin-4-yl)-1H-benzo[b][1,4] diazepine-7-carboxamide (4h): Yield 73 % ; m.p. 115-120ºC. IR (KBr, cm^{-1}): 3395 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd,1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10 H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 547 (M^+). C H N Analysis: Calcd. for $C_{29}H_{31}N_4O_2Br$: C, 63.62; H, 5.71; N, 10.23. Found: C, 63.59; H, 5.68; N, 10.19.

8-Ethoxy-2,3-dihydro-4-phenyl-N-(piperidin-4-yl)-2-*p*-tolyl-1H-benzo[b][1,4]diazepine-7-carboxamide (4i): Yield 66 %; m.p. 180-186ºC. IR (KBr, cm^{-1}): 3395 ν(NH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.1 (s, 3H, CH), 2.3 (d, 2H, CH), 3.8 (q, 1H, CH), 3.9 (dd, 1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 10 H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 483.2 (M^+). C, H, N Analysis: Calcd. for $C_{30}H_{34}N_4O_2$: C, 74.66; H, 7.10; N, 11.61. Found: C, 74.61; H, 7.15; N, 1159.

8-Ethoxy-2,3-dihydro-2,4-diphenyl-N-(piperidin-4-yl)-1H-benzo[b][1,4]diazepine-7-carboxamide (4j): Yield 68 %; m.p. 236-240ºC. IR (KBr, cm^{-1}): 3398 ν(NH). ^1H NMR (DMSO-d_6, δ ppm): 1.0 (t, 3H, CH), 1.4-1.6 (m, 4H, CH), 1.6-1.8 (m, 4H, CH), 2.3 (d, 2H, CH),3.8 (q, 1H, CH), 3.9 (dd,1H, CH), 4.1 (q, 2H, CH), 7.1-7.9 (s, 11 H, Ar-H), 8.1 (s, 1H, Ar-H). Mass: 469.6 (M^+). C, H, N Analysis Calcd. for $C_{29}H_{32}N_4O_2$: C, 74.33; H, 6.88; N, 11.96. Found: C, 74.31; H, 6.83; N, 11.98.

RESULTS AND DISCUSSION

Compounds **4b, 4c, 4d** and **4g** showed significant acceleration in gastric emptying/anti ulcer activity in mice. Cinitapride was used as our reference standard.

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