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Synthesis and Characterization of some 5*H*-dibenzo (*b,f*)azepine-5-carboxamido-4'-aryl-3'-aryl piperazine-2'-azetidinone derivatives

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ABSTRACT

*The synthesis of 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(substituted phenyl)-4-oxo-azetidin-1-yl]-amide **(2a-d)** was achieved by the reaction of **(1a-d)** with chloroacetyl chloride in presence of triethylamine. Three substituted aryl piperazine derivatives **(R_{1-3})** were prepared and they were reacted with **(2a-d)** to give 5H-dibenzo(b,f) azepine-5-carboxamido-4'-aryl-3'-aryl piperazine-2'-azetidinone **(3a-l)**. The products have been characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C-NMR and mass spectral studies.*

Keywords: 5*H*-dibenzo(*b,f*)azepine-5-carboxylic acid (4-methoxy benzylidene)-hydrazide, 5*H*-dibenzo(*b,f*) azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl] amide, 5*H*-dibenzo(*b,f*)azepine-5-carboxamido-4'-(4-methoxyphenyl)-3'-(o-methyl phenyl piperazine)-2'-azetidinone, Substituted aryl piperazine.

INTRODUCTION

A large number of dibenzo(*c,e;b,e;b,f*)azepine have been synthesized and reported to have number of pharmacological activity [1,2,3]. Of this dibenzo(*b,f*)azepine have attracted considerable attention, which shows broad range of pharmaceutically active compounds [3,4,5]. The most common method for the synthesis azetidinones is the Staundinger's ketene-imine reaction [6]. Certain azetidine derivatives of dibenzo(*b,f*) azepines are reported [7,8]. Synthesis of some of aryl piperazine amides and sulfonamides are reported as central nervous system agents [11]. Synthesis of 1-aryl piperazines under microwave irradiation has also been reported [12].

Several aryl piperazine derivatives have been found to pharmacologically active and they have been synthesized and reported by different researchers [13,14]. Certain piperazinly dibenzo(*b,f*)thiepin and dibenzo(*b,f*)oxepins have studied for their therapeutical importance [15].Some dibenzo(*b,f*)azepine derivatives with piperazine skeleton are reported as effective anticancer agents [16]. Some piperazinyl dibenzazepines are also reported to have sedative and antidepressant activity [17]. The objective of the present investigation was to develop a series of new compounds, which may be explored for developing pharmaceutically important molecules. The authors have reported in their previous paper the synthesis of 5*H*-dibenzo(*b,f*)azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl] amide [18]. In the present paper is reported the synthesis and characterization of different 5*H*-dibenzo(*b,f*)azepine-5-carboxamido-4'-aryl-3'-aryl piperazine-2'-azetidinone **3a-l (Scheme I)** from 5*H*-dibenzo(*b,f*)

azepine-5-carboxylic acid [3-chloro-2-(substituted phenyl)-4-oxo-azetidin-1-yl]-amide [15] **2a-d**, and aryl piperazine. All synthesized compounds were characterized by elemental analysis, IR, NMR, ^{13}C-NMR and mass spectrometric (MS) techniques.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. All the chemicals and solvents used were of Laboratory Grade and solvents were purified by suitable methods. IR spectra were recorded on a Shimadzu-8400 FT-IR spectrometer using KBr disc. ^{1}H NMR spectra were recorded on a Brucker 300MHz spectrometer using TMS as an internal standard in $CDCl_3$ and DMSO-d_6, ^{13}C-NMR spectra were recorded on DPX 200 Brucker FT-NMR, mass spectra on a Hewlett-Packard 5989, Quadrapole Mass Spectrometer and LC-MS on a Perkin Elmer API 165. The Elemental analysis was performed on a Perkin Elmer 2400 Series II instrument and found to be satisfactory.

General procedure for the Preparation of 5*H*-dibenzo(*b,f*)azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl]-amide 2a-d. A solution of 5*H*-dibenzo(*b,f*)azepine-5-carboxylicacid-(substituted benzylidene)-hydrazide **1a-d** (0.01 mole) in dry dimethylformamide was added to a well stirred mixture of chloroacetyl chloride (0.012 mole) and triethylamine (0.012 mole) at 0^{o}C and then stirred for 12-24 hours and kept overnight at room temperature. The contents were poured in crushed ice with stirring and the obtained product was filtered, washed with water and dried. The product was recrystallized from suitable solvent.

5*H*-dibenzo(*b,f*)azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl] amide 2a: Orange crystals, Yield 68%, m.p 182 ^{o}C, (Found : C, 67.30; H, 4.47; N, 9.40 Calcd. for $C_{25}H_{20}$ ClN_3O_3: C, 67.34; H, 4.48; N, 9.42%; **(2a)**, IR (KBr): 3359 (NH), 3008 (Ar C-H), 2964 and 2852 (CH_3, C-H), 1745 and 1714 (C=O, β-lactam ring), 1697 and 1681 (NH-C=O), 1506, 1361 (C-N), 1261, 1026 (C-O), 692 (C-Cl);

(2a) : ^{1}H NMR ($CDCl_3$): δ 8.67 (s, 1H, -NH), 7.75 (d, J= 7.60 Hz, 2H, *p*-OCH_3 phenyl ring), 7.69-7.19 (m, 8H, Ar-H), 7.17 (s, 2H, CH=CH), 6.90 (d, J=7.75 Hz, 2H, 4-OCH_3 phenyl protons), 6.74 (d, J=10.51 Hz, 1H, Ar-CH-N), 4.87 (d, J=10.19 Hz, 1H, N-CH-Cl), 3.86 (s, 3H, -OCH_3), **(2a)**: MS : m/z(%) 446 (12.4,M^+), 254 (46.8, M^+), 220 (18.7, M^+), 192 (100), 177 (10.9), 134 (20), **(2a)**: ^{13}C NMR ($CDCl_3$): 167.4 (C=O, Azetidinone ring), 162.5 (hydrazone C=O), 138.9; 138.1; 134.3; 133.9; 131.0; 130.4; 129.7; 129.4; 129.1; 128.7; 126.5 (Aromatic C), 145.6 (CH-Cl of azetidinone ring), 115.0 (Azetidine ring –CH), 56.1 (-O CH_3).

The Elemental and NMR Spectral data of **2a-d** are tabulated in **Table I**

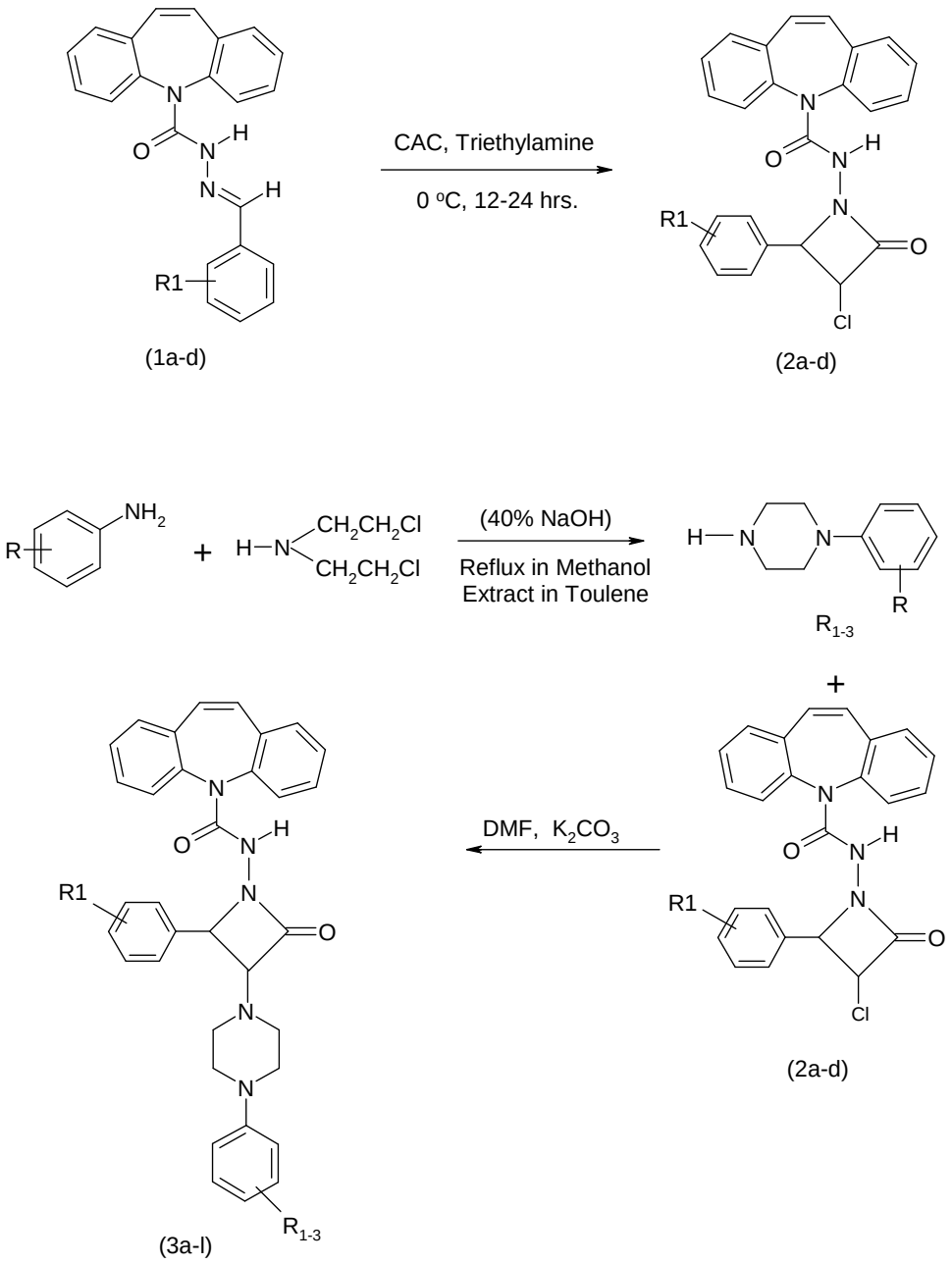
General Procedure for the preparation of Substituted aryl piperazine R_{1-3}
(R_1=*o*-methyl phenyl piperazine; R_2=*m*-Chloro phenyl piperazine; R_3=*p*-Hydroxy phenyl piperazine) Different aromatic amines such as *o*-methyl aniline, *m*-chloro aniline and *p*-hydroxy aniline (0.1 mole) were taken along with bis-(2-chloro-ethyl)-amine (0.14 mole) in water methanol (1:1) and carefully 40%NaOH was added until pH-6, the contents were refluxed for two hours until pH-7 is achieved. Concentrated NaOH was added to the reaction mixture until it is completely alkaline (pH-12). The contents were taken in separating funnel and then extracted with toluene. The toluene layer was distilled and pale colored liquid was obtained. This liquid was taken in isopropyl alcohol and dry HCl gas was passed, to get the corresponding hydrochloride salt.

General procedure for the preparation of 5*H*-dibenzo(*b,f*)azepine-5-carboxamido-4'-aryl-3'-aryl piperazine-2'-azetidinone 3a-l. To a well stirred solution of substituted aryl piperazine (0.013 mole) in 20 ml. of acetone, minimum quantity of anhydrous potassium carbonate (0.019 mole), was added along with **2a-d** (0.013 mole) dissolved in small amount of acetone. After stirring for 0.5 hr, the reaction mixture was kept under reflux for 10 hr on a water bath. The contents were then poured in cold water, extracted with chloroform, and the solvent was evaporated under vacuum to get the product. Yield 38-54%

5*H*-dibenzo(*b,f*)azepine-5-carboxamido-4'-(4-methoxyphenyl)-3'-(*o*-methylphenyl piperazine)-2'-azetidinone (3a), Light yellow colored compound, Yield 68%, m.p 148 ^{o}C, (Found : C, 67.30; H, 4.47; N, 9.40 Calcd. for $C_{25}H_{20}$ ClN_3O_3: C, 67.34; H, 4.48; N, 9.42%; **(3a)**, IR (KBr): 3359 (NH), 3008 (Aromatic C-H stretch), 2964 and 2852 (Methyl C-H Stretch), 1697 and 1681 (C=O), 1745 and 1714 (C=O, β-lactam ring), 1506 (C-N of N-CH-Ar), 1361 (C-N Stretch), 1261 (C-O-C Asymmetric Stretch), 1026 (C-O-C Symmetric Stretch); **(3a)**,^{1}H NMR ($CDCl_3$): δ

8.67 (s, 1H, -NH), 7.17 (s, 2H, CH=CH), 7.13 (1H, d, aryl piperazine , J=7.3, 8.0 Hz), 6.88 to 7.42 (m, 12H, Ar-H), 6.75 (1H, d, Ar-CH, J=9.0Hz), 4.21 (1H, d, CH-N of piperazine, J=9.0Hz), 6.96 (1H, m, aryl piperazine), 6.91 (1H, d, aryl piperazine, J=7.3, 8.0Hz) , 3.87 (s, 3H, -OCH_3), 3.50 (s, 8H, 4-CH_2 of piperazine), 2.16 (s, 3H, *o*-CH_3 aryl piperazine); **(3a)**, LC-MS: 585.2 (M), 410 (M^+), 369 (M^+), 235 (M), 262 (M^+), 220 (M^+), 193 (M^+), 175 (M+2), 84 (M); **(3a)**, ^{13}C NMR ($CDCl_3$): 167.4 (C=O, Azetidinone ring), 162.5 (hydrazone C=O), 138.6; 138.1; 134.6; 133.9; 131.2; 130.7; 129.7; 129.4; 129.1; 128.7; 126.4; 121.7; 121.2; 120.0, 145.1 (CH-N of azetidinone ring), 115.6 (Azetidine ring –CH), 57.8; 57.4 (C of piperazine ring), 56.0 (-O CH_3), 13.1 (*o*-tolyl C).

The Elemental and NMR Spectral data of **3a-l** are tabulated in **Table II, III** & **IV**.



Scheme I-5*H*-dibenzo(*b,f*)azepine-5-carboxamido-4'-Aryl-3'-Aryl piperazine-2'- azetidinone 3a-l.

Table I: Elemental & NMR Spectral data of 2a-d.

Co.	R 1	M.P. (ºC)	Molecular Formula	Found & (Calculated) % C	%H	%N	^{1}H-NMR ($CDCl_3$ & DMSO-d_6) (δ ppm)
2a	4- OCH_3	182	$C_{24}H_{18}N_3O_3Cl$	67.15 (67.34)	4.47 (4.52)	9.35 (9.42)	δ 8.67 (s, 1H, -NH), 7.75 (d, J= 7.60 Hz, 2H, p-OCH_3 phenyl ring), 7.69-7.19 (m, 8H, Ar-H), 7.17 (s, 2H, CH=CH), 6.90 (d, J=7.75 Hz, 2H, 4-OCH_3 phenyl protons), 6.74 (d, J=10.51 Hz, 1H, Ar-CH-N), 4.87 (d, J=10.19 Hz, 1H, N-CH-Cl), 3.86 (s, 3H, -OCH_3).
2b	4-Cl	160	$C_{24}H_{17}N_3O_2Cl_2$	64.20 (64.01)	3.78 (3.81)	9.25 (9.33)	δ8.52 (s, 1H, -NH), 7.88-6.80 (m, 8H, Ar-H + 4H, 4-Cl phenyl ring), 7.10 (s, 2H, CH=CH), 6.66 (d, J=10.50 Hz, 1H, Ar-CH-N), 4.86 (d, J=10.20 Hz, 1H, N-CH-Cl).
2c	4-OH	184	$C_{25}H_{20}N_3O_3Cl$	66.98 (66.75)	4.12 (4.20)	9.65 (9.73)	δ 8.62 (s, 1H, -NH), 7.80-6.90 (m, 8H, Ar-H + 4H, 4-OH phenyl ring), 6.95 (s, 2H, CH=CH), 6.75 (d, J=10.50 Hz, 1H,Ar-CH-N), 4.85 (d, J=10.22 Hz, 1H, N-CH-Cl), 3.40 (s, 1H, -OH).
2d	H	172	$C_{24}H_{18}N_3O_2Cl$	69.54 (69.39)	4.28 (4.33)	10.09 (10.12)	δ 8.66 (s, 1H, -NH), 7.80 (m, 8H, Ar-H +5H, phenyl ring), 6.85 (s, 2H, CH=CH), 6.72 (d, J=10.45 Hz, 1H, Ar-CH-N), 4.83 (d, J=10.20 Hz, 1H, N-CH-Cl).

Table II: Elemental & NMR Spectral data of 3a-d.

Co.	R_1	R 1	M. P (ºC)	Molecular Formula	Found & (Calculated) % C	%H	%N	^{1}H-NMR ($CDCl_3$ & DMSO-d_6) (δ ppm)
3a	*o*-CH_3	4-OCH_3	148-151	$C_{36}H_{35}N_5O_3$	74.05 (73.82)	5.96 (6.02)	11.85 (11.96)	δ 8.85 (s, 1H,-NH), 7.42-6.88 (m, 16H, Ar-H), 7.17 (s, 2H, CH=CH), 6.75 (d, 1H, Ar-CH), 4.21 (d, 1H, CH -N), 3.87 (s, 3H, -OCH_3), 3.50 (s, 8H, 4 -CH_2 of piperazine), 2.16 (s, 3H, -CH_3).
3b	*o*-CH_3	4-Cl	170-173	$C_{35}H_{32}N_5O_2Cl$	70.98 (71.24)	5.36 (5.47)	11.75 (11.87)	δ 8.86 (s, 1H,-NH), 7.40 -6.88 (m, 16H, Ar-H), 7.22 (s, 2H, CH=CH), 6.73 (d, 1H,Ar-CH), 4.20 (d, 1H, CH -N), 3.50 (s, 8H, 4-CH_2 of piperazine), 2.10 (s, 3H, -CH_3).
3c	*o*-CH_3	4-OH	192-195	$C_{35}H_{32}N_5O_3$	73.22 (73.53)	5.72 (5.82)	12.10 (12.25)	δ 8.80(s, 1H, -NH), 7.42-6.88 (m, 16H, Ar-H), 7.10 (s, 2H, CH=CH), 6.72 (d, 1H, Ar-CH),4.20 (d, 1H, CH-N), 3.55 (s, 8H, 4-CH_2 of piperazine), 3.80 (s, 1H, -OH), 2.10 (s, 3H, -CH_3).
3d	*o*-CH_3	H	160-165	$C_{35}H_{33}N_5O_2$	74.98 (75.65)	5.96 (5.99)	12.55 (12.60)	δ 8.86 (s, 1H, -NH), 7.40-6.80 (m, 17H, Ar-H), 7.22 (s, 2H, CH=CH), 6.75 (d, 1H,Ar-CH), 4.21 (d, 1H,CH -N), 3.52 (s, 8H, 4-CH_2 of piperazine), 2.14 (s, 3H, -CH_3).

Table III: Elemental & NMR Spectral data of 3e-h.

Co.	R_2	R 1	M. P (ºC)	Molecular Formula	Found & (Calculated) %H	%N	% C	^{1}H-NMR ($CDCl_3$ & DMSO-d_6) (δ ppm)
3e	*m*-Cl	4-OCH_3	152-155	$C_{35}H_{32}N_3O_5Cl$	69.78 (69.36)	5.25 (5.32)	11.42 (11.55)	δ 8.86 (s, 1H, -NH), 7.40-6.88 (m, 16H, Ar-H), 7.10 (s, 2H, CH=CH), 6.71 (d, 1H, Ar-CH), 4.10 (d, 1H, CH-N), 3.86 (s, 3H, -OCH_3), 3.55 (s, 8H, 4-CH_2 of piperazine).
3f	*m*-Cl	4-Cl	178-180	$C_{34}H_{29}N_5O_2Cl_2$	66.55 (66.89)	4.62 (4.79)	11.39 (11.47)	δ 8.82 (s, 1H, -NH), 7.40-6.80 (m, 16H, Ar-H), 7.15 (s, 2H, CH=CH), 6.72 (d, 1H,Ar-CH), 4.20 (d, 1H, CH-N), 3.54 (s, 8H, 4-CH_2 of piperazine).
3g	*m*-Cl	4-OH	180-182	$C_{34}H_{30}N_5O_3Cl$	68.75 (68.97)	5.02 (5.11)	11.73 (11.83)	δ 8.82 (s, 1H, -NH), 7.45-6.85 (m, 16H, Ar-H), 7.10 (s, 2H, CH=CH), 6.76 (d, 1H,Ar-CH), 4.12 (d, 1H, CH-N), 3.88 (s, 1H, -OH), 3.51 (s, 8H, 4-CH_2 of piperazine).
3h	*m*-Cl	H	166-168	$C_{34}H_{30}N_5O_2Cl$	70.55 (70.89)	5.12 (5.25)	12.10 (12.16)	δ 8.80 (s, 1H, -NH), 7.40-6.80 (m, 17H, Ar-H), 7.20 (s, 2H, CH=CH), 6.74-6.70 (d, 1H,Ar-CH), 4.22-4.11 (d, 1H, CH-N), 3.50 (s, 8H, 4-CH_2 of piperazine).

Table IV: Elemental & NMR Spectral data of 3i-l.

Co.	R_3	R 1	M. P (ºC)	Molecular Formula	Found & (Calculated) % C	%H	%N	^{1}H-NMR ($CDCl_3$ & DMSO-d_6) (δ ppm)
3i	*p*-OH	4-OCH_3	159-162	$C_{35}H_{33}N_5O_4$	71.88 (71.53)	5.35 (5.66)	11.77 (11.92)	δ 8.80 (s, 1H, -NH), 7.24-6.88 (m, 16H, Ar-H), 7.10 (s, 2H, CH=CH), 6.74 (d, 1H, Ar-CH), 4.15 (d, 1H, CH-N), 4.42 (s, 1H, Ph-OH, with piperazine ring), 3.85 (s, 3H, -OCH_3), 3.50 (s, 8H, 4-CH_2 of piperazine).
3j	*p*-OH	4-Cl	151-153	$C_{34}H_{30}N_5O_3Cl$	68.71 (68.97)	5.02 (5.11)	11.75 (11.83)	δ 8.82 (s, 1H, -NH), 7.40-6.85 (m, 16H, Ar-H), 7.18 (s, 2H, CH=CH), 6.72 (d, 1H,Ar-CH), 4.24 (d, 1H, CH-N), 4.45 (s, 1H, Ph-OH with piperazine), 3.56 (s, 8H, 4-CH_2 of piperazine).
3k	*p*-OH	4-OH	176-178	$C_{34}H_{31}N_5O_4$	71.02 (71.19)	5.32 (5.45)	12.11 (12.21)	δ 8.80 (s, 1H, -NH), 7.42-6.88 (m, 16H, Ar-H), 7.20 (s, 2H, CH=CH), 6.76 (d, 1H,Ar-CH), 4.08 (d, 1H, CH-N), 4.40 (s, 1H, Ph-OH, with piperazine ring), 3.80 (s,1H, Ar-OH), 3.50 (s, 8H, 4-CH_2 of piperazine).
3l	*p*-OH	H	142-145	$C_{34}H_{31}N_5O_3$	73.01 (73.23)	5.52 (5.60)	12.55 (12.56)	δ 8.80 (s, 1H, -NH), 7.45-6.80 (m, 17H, Ar-H), 7.20 (s, 2H, CH=CH), 6.70 (d, 1H, Ar-CH), 4.10 (d, 1H, CH-N), 4.42 (s, 1H, Ph-OH, with piperazine ring), 3.50 (s, 8H, 4-CH_2 of piperazine).

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