13. List of publication


3. *Vimal Patel and H D Joshi.*; Synthesis and antimicrobial evaluation of novel 2-aryl thiaazolidinones (under communication-Pharmaceutical chemistry journal)

4. *Vimal Patel and H D Joshi.*; Novel derivatives of 5,6-dimethoxy indanone coupled with substituted pyridine as potential antimicrobial agents (under communication-Arabian journal of chemistry)

5. *Vimal Patel and H D Joshi.*; Synthesis and pharmacological evaluation of novel 1-(piperidin-4-y1)-1h-benzo[d]imidazol-2(3h)-one derivatives as potential antimicrobial agents (under communication-Medicinal chemistry research journal)
Synthesis and Characterization of some 5H-dibenzo (b,f)azepine-5-carboxamido-4’-aryl-3’-aryl piperazine-2’-azetidinone derivatives

Vimal Patel¹, Nilay D Bhatt, Pravin M. Patel², Pralav Bhatt³ and H D Joshi¹

¹Department of Chemistry, Saurashtra University, Rajkot, Gujarat, India
²Industrial Chemistry Department, V.P. & R.P.T.P Science College, Vallabh Vidyanagar, Anand, Gujarat, India
³School of Chemistry, University of KwaZulu-Natal, Westville Campus, Durban, South Africa

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 (R₁-3) 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, ¹H NMR, ¹³C-NMR and mass spectral studies.

Keywords: 5H-dibenzo(b,f)azepine-5-carboxylic acid (4-methoxy benzylidene)-hydrazide, 5H-dibenzo(b,f) azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl] amide, 5H-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;h,e;h)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 Stauninger’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 piperazinyl 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 5H-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 5H-dibenzo(b,f)azepine-5-carboxamido-4′-aryl-3′-aryl piperazine-2′-azetidinone 3a-l (Scheme 1) from 5H-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, Quadrupole 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 5H-dibenzo(b,f)azepine-5-carboxylic acid [3-chloro-2-(4-methoxy phenyl)-4-oxo-azetidin-1-yl]-amide 2a-d**

A solution of 5H-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 $\beta$-chloro acetyl chloride (0.012 mole) and triethylamine (0.012 mole) at 0°C 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%.

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, Quadrupole 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 Substituted aryl piperazine R$_1$-3 (R$_1$=o-methyl phenyl piperazine; R$_2$=Cl-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 5H-dibenzo(b,f)azepine-5-carboxamido-4'-aryl-3'-aryl piperazine-2'-azetidinone 3a-l**

Light yellow colored compound. Yield 68%. m.p 148°C, (Found : C, 67.30; H, 4.47; N, 9.40. Calcd. for C$_2$_H$_2$_N$_2$O$_4$: C, 67.34; H, 4.48; N, 9.42%; (3a) IR (KBr): 3359 (NH), 3008 (Aromatic C-H stretch), 2964 and 2852 (CH$_3$, CH$_2$), 167.4 (C=O, Azetidinone ring), 162.5 (Aromatic C-N of N-CH-Ar), 4.87 (d, J=10.19 Hz, 1H, Ar-CH-N), 3.86 (s, 3H, -OCH$_3$ piperazine). All synthesized compounds were characterized by elemental analysis, IR, NMR, mass spectrometric (MS) techniques.
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-5H-dibenzo(b,f)azepine-5-carboxamido-4’-Aryl-3’-Aryl piperazine-2’-azetidinone 3a-l.](image)

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

<table>
<thead>
<tr>
<th>Co.</th>
<th>R</th>
<th>M.P. (°C)</th>
<th>Molecular Formula</th>
<th>Found % &amp; (Calculated)</th>
<th>¹H-NMR (CDCl₃, &amp; DMSO-d₆) (δ ppm)</th>
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<tr>
<td>2a</td>
<td>4-Cl</td>
<td>182</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
<td>67.75 (67.34)</td>
<td>4.47 (4.52) 9.35 (9.42)</td>
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<tr>
<td>2b</td>
<td>4-Cl</td>
<td>160</td>
<td>C₂₆H₂₆N₈O₈Cl₂</td>
<td>64.20 (64.01)</td>
<td>3.78 (3.81) 2.95 (2.93)</td>
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<tr>
<td>2c</td>
<td>4-OH</td>
<td>184</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
<td>66.98 (66.75)</td>
<td>4.12 (4.20) 9.65 (9.73)</td>
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<tr>
<td>2d</td>
<td>H</td>
<td>172</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
<td>69.54 (69.39)</td>
<td>4.28 (4.33) 10.09 (10.12)</td>
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Table II: Elemental & NMR Spectral data of 3a-d.

<table>
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<th>R₂</th>
<th>M.P. (°C)</th>
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<tr>
<td>3a</td>
<td>o-CH₃</td>
<td>4-OCH₃</td>
<td>148-151</td>
<td>C₂₆H₂₆N₈O₈</td>
<td>74.05 (73.85)</td>
<td>5.96 (6.02) 11.85 (11.96)</td>
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<td>3b</td>
<td>o-CH₃</td>
<td>4-Cl</td>
<td>170-173</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
<td>70.98 (71.24)</td>
<td>5.36 (5.47) 11.75 (11.87)</td>
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<td>192-195</td>
<td>C₂₆H₂₆N₈O₈</td>
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<td>5.72 (5.82) 12.10 (12.25)</td>
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<td>H</td>
<td>160-165</td>
<td>C₂₆H₂₆N₈O₈</td>
<td>74.98 (75.65)</td>
<td>5.96 (5.99) 12.55 (12.60)</td>
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Table III: Elemental & NMR Spectral data of 3e-h.

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<th>Co.</th>
<th>R₂</th>
<th>R₁</th>
<th>M.P. (°C)</th>
<th>Molecular Formula</th>
<th>Found % &amp; (Calculated)</th>
<th>¹H-NMR (CDCl₃, &amp; DMSO-d₆) (δ ppm)</th>
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<tr>
<td>3e</td>
<td>m-Cl</td>
<td>4-OCH₃</td>
<td>152-155</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
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<td>m-Cl</td>
<td>4-Cl</td>
<td>178-180</td>
<td>C₂₆H₂₆N₈O₈Cl₂</td>
<td>66.55 (66.89)</td>
<td>4.62 (4.79) 11.39 (11.47)</td>
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<td>4-OH</td>
<td>180-182</td>
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<td>68.75 (68.97)</td>
<td>5.02 (5.11) 11.73 (11.83)</td>
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<tr>
<td>3h</td>
<td>m-Cl</td>
<td>H</td>
<td>166-168</td>
<td>C₂₆H₂₆N₈O₈Cl</td>
<td>70.55 (70.89)</td>
<td>5.12 (5.25) 12.10 (12.16)</td>
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</table>
Table IV: Elemental & NMR Spectral data of 3i-l.

<table>
<thead>
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<th>Co.</th>
<th>R1</th>
<th>R</th>
<th>M. P (°C)</th>
<th>Molecular Formula</th>
<th>Found &amp; (Calculated)</th>
<th>$^1$H-NMR (CDCl$_3$ &amp; DMSO-d$_6$) (δ ppm)</th>
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</thead>
<tbody>
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<td>3i</td>
<td>p-</td>
<td>OH</td>
<td>159-162</td>
<td>C$_6$H$_3$N$_2$O$_4$</td>
<td>71.88 &amp; (71.53) 5.35 &amp; (5.66) 11.77 &amp; (11.92)</td>
<td>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).</td>
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<tr>
<td>3j</td>
<td>p-</td>
<td>OH</td>
<td>151-153</td>
<td>C$_6$H$_3$N$_2$O$_4$Cl</td>
<td>71.02 &amp; (71.19) 5.32 &amp; (5.45) 12.11 &amp; (12.21)</td>
<td>δ 8.80 (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).</td>
</tr>
<tr>
<td>3k</td>
<td>p-</td>
<td>OH</td>
<td>176-178</td>
<td>C$_6$H$_3$N$_2$O$_4$</td>
<td>73.01 &amp; (73.23) 5.52 &amp; (5.60) 12.55 &amp; (12.68)</td>
<td>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).</td>
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Acknowledgements

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REFERENCES