SYNTHESIS, ANTICANCER AND ANTITUBERCULOSIS STUDIES FOR [1-(4-CHLOROPHENYL) CYCLOPROPYL] (PIPERAZINE-YL) METHANONE DERIVATES

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ABSTRACT

Objective: Synthesis, anticancer and antituberculosis studies for 1-(4-Chlorophenyl) cyclopropyl] (piperazin-1-yl) methane derivatives 3a-j

Methods: A series of new 1-(4-Chlorophenyl) cyclopropyl] (piperazin-1-yl) methane derivatives were synthesized using reductive amination method in presence of sodium triacetoxyborohydride to yield piperazine derivatives 3a-j. The structures of all newly synthesized compounds have been characterised by elemental analysis and spectral studies.

Results: Five selected compounds have been screened for in vitro anticancer activity against human breast cancer cell line MDA-MB-435 at 10, 20, 40 and 80 µg/mL concentration using sulforhodamine B assay method. and Two compounds 3a and 3c have shown in vitro antituberculosis activity.

Conclusion: Synthesis of [1-(4-Chlorophenyl) cyclopropyl] (piperazin-1-yl) methane derivatives 3a-j simple and convenient method. Some of the tested compounds have exhibited significant antituberculosis and anticancer activity. Compound 3c showed both antituberculosis and anticancer activity.

Keywords: Piperazine, Aldehydes, Cyclopropane, Antituberculosis, Anticancer.

INTRODUCTION

Disubstituted piperazines exhibit wide range of biological properties as reported in the literature. In the last decade, a number of piperazine derivatives have been synthesized and evaluated for their cytotoxic activity [1-4]. Additional clinical drug development studies of the piperazine compounds in small-animal models by the US National Cancer Institute (NCI) demonstrated that these targets had the ability to suppress experimental tumours.

As a result of the study for the lead compounds, It has been reported that inhibitory action was observed against colon, prostate, breast, lung and immune cell tumours in many indole carrying small anti cancer molecules [5]. In addition, piperazines have been found to posses several biological activities [6-11] including antituberculosis activity [12]. The polarity of nitrogen atoms of piperazine ring enhances favourable interaction with bio macromolecules and thus confers the biological activity [13-14]. Thus, based on these observations in the literature, the present study was initiated with aim of identifying the structural requirements of piperazines in terms of anticancer and antitubercular activity.

MATERIALS AND METHODS

Chemistry

All the chemicals and solvents used in this work were of analytical reagent grade (anhydrous) and purchased from Sigma-Aldrich. All the IR spectra were recorded on Bruker alpha FTIR spectrophotometer, ¹H NMR spectra were measured on Bruker AV 400MHZ using CDCl₃ and DMSO as solvent. Chemical shifts are expressed in δ ppm.

Elemental Analysis was performed on an Elementar Vario EL elemental analyzer. Satisfactory C, H, N analyses were obtained for all the compounds. All the reactions were followed and checked by TLC (silica coated on alumina) using ethylacetate-pet ether (3:7) and further purification was done by column chromatography using 60-120 mesh silica gel.

Scheme 1: Synthesis of piperazine methanone derivatives 3a-j.

1. t-Butyl 4-(1-(4-Chlorophenyl) cyclopropanecarboxyl) piperazine-1-carboxylate (1)

1-(4-Chlorophenyl) cyclopropanecarboxylic acid (2.00 g, 0.0102 mol) was dissolved in dry tetrahydrofuran (20 mL). The solution...
was stirred for 10 min at ambient temperature. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.15 g, 0.01122 mol) was added, followed by 1-hydroxybenzotriazole (1.718 g, 0.01122 mol) and N,N-diisopropylethylamine (3.955 g, 0.0305 mol). The reaction mixture was stirred for 20 min at ambient temperature, and then it was cooled to 0°C. Boc-tert-butyloxycarbonyl (tert-butyloxycarbonyl) piperazine-1-carboxylate (1) was dissolved in toluene (7.40 g, 0.0102 mol) to form a solution. The reaction mixture was cooled to 0°C and stirred for 20 min at ambient temperature. The completion of the reaction was monitored by TLC. The reaction mixture and stirring was continued for 6 h at ambient temperature.

The completion of the reaction was monitored by TLC. The reaction mixture was filtered and washed with hexane to get 3.4 g of t-butyl 4-((1-chlorophenyl)cyclopropyl) piperazine-1-carboxylate (1).

LC-MS (ESI, Positive): m/z: [M+H] +: 365.2

m/z: [M+H] +: 265.2

cyclopropanecarbonyl) piperazine-1-carboxylate (1).

LC-MS (ESI, Positive): m/z: [M+H] +: 394.9;

Dichloromethane (20 mL) and the reaction mixture was cooled to 0°C. The reaction mixture was stirred for 20 min at ambient temperature, then it was cooled to 0°C. Boc-piperazine (1.718 g, 0.01122 mol) and 1-hydroxybenzotriazole (1.718 g, 0.01122 mol) was added, followed by sodium triacetoxyborohydride (0.557g,0.002632 mol) and Glacial acetic acid (0.01122 mol) and triethylamine (3.955 g,0.0305 mol). Substituted aldehydes(0.0020 mol) was added, followed by sodium triacetoxyborohydride (0.557g,0.002632 mol) and Glacial acetic acid (0.01122 mol) and triethylamine (3.955 g,0.0305 mol). The reaction mixture was heated at 65 -700C for 12 -14 hr. The completion of reaction was monitored by TLC. The reaction mixture was heated at 65 -700C for 12 -14 hr. The completion of reaction was monitored by TLC. The reaction mixture was heated at 65 -700C for 12 -14 hr. The completion of reaction was monitored by TLC. The reaction mixture was washed with water (15 mL), brine (15 mL) and dried over sodium sulphate. The organic layer was dried over anhydrous sodium sulphate. The organic layer was evaporated under reduced pressure and the crude reaction mixture obtained was purified by column chromatography using 60-120 mesh silica gel and 10% ethyl acetate in hexane to get 3.4 g of t-butyl 4-((1-chlorophenyl)cyclopropyl) piperazine-1-carboxylate (1). The crude reaction mixture was purified by column chromatography using silica gel and 10% ethyl acetate in hexane to get 3.4 g of t-butyl 4-((1-chlorophenyl)cyclopropyl) piperazine-1-carboxylate (1).

2. [1-(4-Chlorophenyl)cyclopropyl]piperazine-1-yl)methanone (2)

Compound 1 (3.4 g, 0.00934 mol) was dissolved in dry Dichloromethane (20 mL) and the reaction mixture was cooled to 0°C. The crude reaction mixture obtained was purified by column chromatography using silica gel and 10% ethyl acetate in hexane to get 3.4 g of t-butyl 4-((1-chlorophenyl)cyclopropyl) piperazine-1-carboxylate (1).

3. 1-(4-Chlorophenyl)cyclopropyl (4-(pyridin-3-ylmethyl)piperazin-1-yl)methanone (3b)

The crude reaction mixture was purified by column chromatography using silica gel and 10% ethyl acetate in hexane to get 3.4 g of t-butyl 4-((1-chlorophenyl)cyclopropyl) piperazine-1-carboxylate (1).

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 394.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;

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LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

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LC-MS (ESI, Positive): m/z: [M+H] +: 406.1;

LC-MS (ESI, Positive): m/z: [M+H] +: 345.8;

LC-MS (ESI, Positive): m/z: [M+H] +: 406.9;

LC-MS (ESI, Positive): m/z: [M+H] +: 356.8;
Table 1: Synthesis of piperazine methanone derivatives 3a-j

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3.9. 1-(4-Chlorophenyl) cyclopropyl) (4-((4,5-dimethylfuran-2-yl)methyl)piperazin-1-yl)methanone (3i):

LC-MS (ESI, Positive): m/z: [M+H] +: 373.8; 1H NMR (400 MHz, DMSO-d6): δ 7.39-7.34 (m, 2H), 7.19-7.14 (m, 2H), 5.59 (s, 1H), 3.65 (s, 2H), 3.46-3.39 (m, 4H), 2.23-2.11 (m, 4H), 2.10 (s, 3H), 1.92 (s, 3H), 1.19-1.15 (m, 2H).

13C NMR (400 MHz, DMSO-d6): δ 169.62, 148.62, 146.59, 140.44, 131.13, 129.01, 127.54, 114.39, 112.51, 54.30, 52.06, 29.10, 15.68; IR
Table 2: Anticancer activity against Human Breast Cancer Cell Line MDA-MD-435

<table>
<thead>
<tr>
<th>Drug Concentration (µg/ml)</th>
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<th>Experiment 2</th>
<th>Experiment 3</th>
<th>Average Values</th>
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<tbody>
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Table 3: Parameter study table (LC50, TGI, and GI50)

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<th>GI50</th>
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<tr>
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<td>59.4</td>
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<td>11.7</td>
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<tr>
<td>3d</td>
<td>&gt;80</td>
<td>&gt;80</td>
<td>66.9</td>
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<td>&gt;80</td>
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<tr>
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<td>&lt;10</td>
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</table>

CONCLUSION

The research work focused on the efficient synthesis of cyclopropyl piperezine derivatives. The reactions performed are eco-friendly. In addition, some of the tested compounds have exhibited significant antituberculosis and anticancer activity. The publication of these facts would be of significant use for the scientific community. Some selected cyclopropyl piperezine derivatives have been tested for antituberculosis and in vitro anticancer activity. Recommended compounds have been under development.
screen for *in vivo* anticancer activity. Compound 3c showed both antituberculosis and anticancer activity.

**CONFLICT OF INTERESTS**

Declared None

**ACKNOWLEDGEMENT**

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**REFERENCES**