

## SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF HYDRAZONES DERIVED FROM IBUPROFEN

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### ABSTRACT

Thirteen new hydrazones **5a-m** were prepared from commercially available Ibuprofen. The structures of the synthesized hydrazones were determined by the spectroscopic techniques like <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass and IR spectral data. These compounds were screened against two Gram negative and two Gram positive bacteria viz., *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* respectively. Compounds **5h**, **5i**, **5j**, **5k**, **5l** and **5m** exhibited good antibacterial activity compared to the standard drug Norfloxacin.

**KEYWORDS:** Ibuprofen, Hydrazone, Synthesis, Antibacterial activity.

### INTRODUCTION

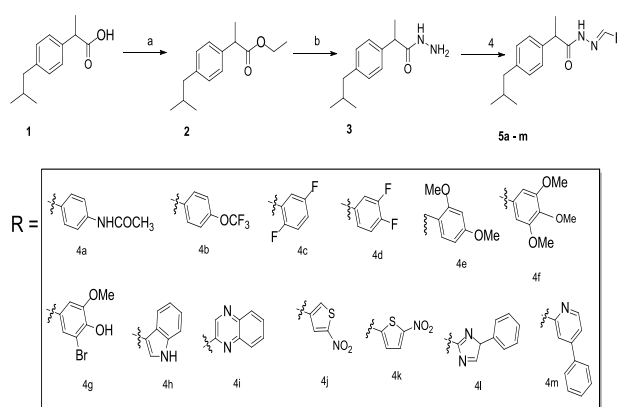
Hydrazones are the important organic functional groups, possessing an azomethine proton (-NHN=CH-), for the construction of a new class of compounds for drug development. Hydrazones exhibit a wide range of biological activities like antitubercular, antiviral, antibacterial, antitumoral and antimalarial properties.<sup>[1]</sup> They also act as intermediates for the synthesis of several heterocyclic compounds such as oxadiazolines, azetidinones, thiazolidinones and many other derivatives.<sup>[2]</sup> In view of the importance of the hydrazones, many medicinal chemists have synthesized these compounds as well as their metal complexes as target structures and evaluated their biological activities.<sup>[3]</sup>

Regardless of the fast growth of science, the dealing of infectious diseases still remains a solemn problem of apprehension to the scientific community, largely because of the extensive range of factors foremost to the emergence of these diseases and also the increased number of pathogenic microorganisms with resistance to multiple drugs, including the Gram positive bacteria.<sup>[3-7]</sup>

Ibuprofen is (2RS)-1[4-(2-methylpropyl) phenyl] propionic acid.<sup>[8]</sup> Ibuprofen was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to aspirin. Gastric discomfort, nausea and vomiting are still the most common side effects though less than aspirin or indomethacin.<sup>[9-10]</sup> Ibuprofen is effective in reducing high body temperature, and an anti-inflammatory which inhibits normal platelet function. Ibuprofen is reported to be better for joint and

muscle pain than other pain killer and has been used by people for arthritis for years.

However, synthesis of hydrazone derivatives of ibuprofen and study of their biological activities not explored very well. Therefore, herein we report synthesis of new ibuprofen hydrazones (**Scheme 1**) and their antibacterial activities.



**Scheme 1: Synthesis of hydrazones of Ibuprofen 5a-m.**

**Reaction conditions:** (a) conc.H<sub>2</sub>SO<sub>4</sub>, Ethanol, 10 h, reflux; (b) Hydrazine-hydrate, Ethanol, reflux, 3 h; (R) Aldehydes (**4a-4m**), ethanol, reflux, 1h.

### MATERIALS AND METHODS

Chemicals and solvents were purchased from Sigma-Aldrich and Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized

under UV light. IR spectra were recorded using KBr pellet with a Perkin-Elmer Spectrum GX FTIR instrument and only diagnostic and/or intense peaks are reported. <sup>1</sup>H NMR spectra were recorded in DMSO-*d*<sub>6</sub> with a Varian Mercury plus 500 MHz instrument. All the chemical shifts were reported in  $\delta$  (ppm) using TMS as an internal standard. The <sup>1</sup>H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument.

#### Ethyl- 2-(4-Isobutylphenyl) propanoate (2)

A solution of carboxylic acid **1** (2g, 9.70 mmol) in ethanol (20 mL) was refluxed for 10 h in presence of catalytic conc. H<sub>2</sub>SO<sub>4</sub>. After the completion of the reaction (Monitored by T.L.C), the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 X 10 mL). The organic layer was washed with water (15 mL) followed by brine solution. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure to afford compound **2**. Pale yellow oil; Yield: 1.63 g, 72%. IR (KBr): 3052, 2955, 2829, 2873, 2847, 1741, 1514, 1469, 1439, 1380, 1339, 1273, 1163, 1208, 1098, 1028, 1070, 884, 851, 784, 672, 638, 556, 523 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  7.18 (d, *J* = 6.8 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 3.76 (q, *J* = 6.2 Hz, 1H), 3.58 (q, 3H), 2.40 (d, *J* = 4.8 Hz, 2H), 1.80-1.72 (m, 1H), 1.38 (d, *J* = 4.8 Hz, 3H), 0.82 (d, *J* = 4.8 Hz, 6H); ESI MS: m/z, 221.1 [M + 1].

#### 2-(4-Isobutylphenyl) propanehydrazide (3)

To a stirred solution of compound **2** (1.6 g, 6.82 mmol) in ethanol (20 mL) was added hydrazine hydrate (2.40 g, 48 mmol) and refluxed for 4 h. After completion of the reaction (monitored by T.L.C), ethanol was evaporated and the precipitated solid was diluted with water and filtered at the pump and dried to obtain compound **3**. White solid; Yield: 1.12 g, 75%; IR (KBr): 3310, 3275, 3208, 3178, 3052, 3028, 2955, 2842, 2869, 2955, 1689, 1644, 1540, 1510, 1461, 1420, 1383, 1361, 1383, 1260, 1212, 1171, 1093, 1078, 1098, 970 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  9.12 (brs, 1H), 7.20 (d, *J* = 6.8 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 4.20 (brs, 2H), 3.48-3.42 (m, 1H), 2.35 (d, *J* = 4.8 Hz, 2H), 1.80-1.72 (m, 1H), 1.35 (d, *J* = 4.8 Hz, 3 H), 0.82 (d, *J* = 5.2 Hz, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  177.8, 139.2, 139.1, 128.6 (2C), 126.9, 44.1, 42.8, 29.5, 22.1 (2C), 18.3 (2C); ESI MS: m/z, 221.1 [M + 1].

#### General procedure for the synthesis of hydrazone derivatives (5a-m)

A mixture of compound **3** (100 mg, 0.454 mmol) and aldehydes (**4a-m**) (0.454 mmol) was refluxed in ethanol for 1 h. The reaction mixture was cooled to room temperature and the precipitated solids were filtered and

dried to obtain hydrazone derivatives in quantitative yields (90-95%).

#### (E)-N<sup>1</sup>-(4-Acetamidobenzylidene)-2-(4-isobutylphenyl) propanehydrazide (5a)

White solid; Yield: 152 mg 92%; M.p: 109-109 °C; IR (KBr): 3305, 3245, 3078, 3055, 2955, 2925, 2669, 1659, 1607, 1588, 1551, 1465, 1551, 1514, 1316, 1288, 1208, 1015 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 11.38 (s, 1H), 10.08 (s, 1H), 8.11 (s, 1H), 7.62 (dd, *J* = 2.5, 8.5 Hz, 2H), 7.57 (dd, *J* = 2.0, 8.5 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 8.0, 2H), 4.66-4.60 (m, 1H), 3.6 (d, 1H), 2.50-2.37 (m, 4H), 1.84-1.76 (m, 2H), 1.38 (t, *J* = 6.0 Hz, 3H), 1.26 (s, 3H), 0.85 (d, *J* = 6.0 Hz, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  174.8, 168.4, 146.2, 142.2, 140.8, 139.4, 128.8, 127.5, 118.88, 44.10, 39.9, 29.5, 24.0, 22.10 (2C), 18.4; ESI MS: m/z, 366.2 [M+1] Anal. calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>.

#### (E)-N<sup>1</sup>-(4-(Trifluoromethoxy) benzylidene)-2-(4-isobutylphenyl) propanehydrazide (5b)

White solid; Yield: 160mg 90%; M.p: 89-90 °C; IR (KBr): 3175, 3078, 3026, 2951, 2843, 1666, 1610, 1469, 1417, 1584, 1506, 1387, 1280, 1260, 1160, 1070 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  11.56 (s, 1H), 8.22 (s, 1H), 7.77 (t, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.25 (d, *J* = 6.5 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 2H), 4.63 (d, *J* = 7.0 Hz, 1H), 2.50-2.36 (m, 3H), 1.80-1.76 (m, 1H), 1.38 (t, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  175.1, 149, 144.9, 140.8, 139.5, 139, 133.5, 128.8 (2C), 128.7, 127.2, 121.2, 120.9, 44.16, 40.2, 20.5, 22.0 (2C), 18.4; ESI MS: m/z, 393.1 [M+1] Anal. calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>.

#### (E)-N<sup>1</sup>-(2,5-Difluorobenzylidene)-2-(4-isobutylphenyl)propanehydrazide (5c)

White solid; Yield: 146 mg 94%; M.p: 79-80 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  11.58 (s, 1H), 8.18 (s, 1H), 7.70-7.66 (m, 1H), 7.51-7.46 (m, 2H), 7.26 (t, *J* = .0 Hz, 2H), 7.10-7.06 (m, 4H), 4.63 (brs, 1H) 2.50-2.36 (m, 2H), 1.80-1.75 (m, 1H), 1.39 (t, *J* = 6.0 Hz, 3H), 0.85 (t, *J* = 6.0 Hz, 6H); ESI MS: m/z, 345.1 [M+1] Anal. calcd. for C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>N<sub>2</sub>O.

#### (E)-N<sup>1</sup>-(3,4-Difluorobenzylidene)-2-(4-isobutylphenyl)propanehydrazide (5d)

White solid; Yield: 48 mg 95%; M.p: 96-97 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  11.61 (s, 1H), 8.37 (s, 1H), 7.92-7.87 (m, 1H), 7.34-7.26 (m, 1H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.16-7.06 (m, 2H), 4.60 (d, *J* = 7.0 Hz, 1H), 2.50-1.88 (m, 1H), 1.38-1.35 (d, *J* = 7.5 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>):  $\delta$  175.1, 139.5, 139.0, 138.4, 134.6, 128.9, 127.7, 126.9, 118.6, 112.6, 104.5, 44.1, 40.1, 39.3, 29.5, 22.1, 18.4; ESI MS: m/z, 345.2 [M+1] Anal. calcd. for C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>N<sub>2</sub>O.

**(E)-N'-(2,4-Dimethoxybenzylidene)-2-(4-isobutylphenyl)propanehydrazide (5e)**

White solid; Yield: 150 mg 90%; M.p: 122-123 °C; IR (KBr): 3238, 3216, 3074, 2966, 2838, 1686, 1659, 1603, 1558, 1461, 1420, 1368, 1320, 1279, 1208, 1186, 1160, 1015 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.33 (s, 1H), 8.44 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.10-7.05 (m, 2H), 6.58 (d, *J* = 7.6 Hz, 2H), 4.60 (d, *J* = 7.0 Hz, 1H) 3.80 (s, 6H), 2.37 (s, 2H), 1.79 (m, 1H), 0.85 (t, *J* = 7.0 Hz, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>): δ 174.6, 162.2, 158.9, 141.9, 139.2, 138.2, 128.8, 127.2, 126.4, 115.1, 106.3, 98.2, 55.6, 44.1, 39.9, 22.1, 20.5 (3C), 18.4; ESI MS: m/z, 369.2 [M+1] Anal. calcd. for C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>.

**(E)-N'-(3,4,5-Trimethoxybenzylidene)-2-(4-isobutylphenyl) propanehydrazide (5f)**

White solid; Yield: 166 mg 95%; M.p: 111-112 °C; IR (KBr): 3037, 3197, 3003, 2929, 2889, 2843, 2292, 2109, 2083, 1659, 1666, 1614, 1506, 1454, 1420, 1372, 1331, 1231, 1126 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.44 (s, 1H), 8.12 (s, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.95 (s, 2H), 4.57 (m, 3H), 3.80 (s, 6H), 3.66 (s, 3H), 2.41-2.36 (s, 2H), 1.79-1.76 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 6H); ESI MS: m/z, 399.2 [M+1] Anal. calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>.

**(E)-N'-(3-Bromo-4-hydroxy-5-methoxybenzylidene)-2-(4-isobutylphenyl) propanehydrazide (5g)**

White solid; Yield: 180 mg 92%; M.p: 126-127 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.42 (s, 1H), 9.93 (s, 1H), 8.04 (s, 1H), 7.28-7.07 (m, 6H), 4.56 (brm, 1H), 3.89 (s, 3H), 2.40-2.34 (m, 2H), 1.80-1.73 (m, 1H), 1.35 (t, *J* = 3.5 Hz, 3H), 0.86-0.78 (d, *J* = 10.5 Hz, 6H); ESI MS: m/z, 433.1 [M+1] Anal. calcd. for C<sub>21</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>3</sub>.

**(E)-N'-((1H-Indol-3-yl) methylene)-2-(4-isobutylphenyl) propanehydrazide (5h)**

White solid; Yield: 149 mg 95%; M.p: 131-132 °C; IR (KBr): 3212, 3026, 3108, 2956, 2925, 2869, 1607, 1633, 1567, 1581, 1514, 1443, 1336, 1365, 1288, 1234, 1234, 1128, 1074, 981, 851, 944, cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.58 (brs, 1H), 11.18 (s, 1H), 8.36 (s, 1H), 8.20-8.12 (m, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.44-7.38 (m, 1H), 7.36-7.30 (m, 2H), 7.10-7.0 (m, 3H), 4.76-4.70 (m, 1H), 2.40-2.32 (m, 2H), 1.88-1.70 (m, 1H), 1.42-1.38 (m, 3H), 1.90-1.78 (m, 6H); ESI MS: m/z, 348.2 [M+1] Anal. calcd. for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O.

**(E)-2-(4-Isobutylphenyl)-N'-((quinoxalin-3-yl) methylene) propanehydrazide (5i)**

White solid; Yield: 147 mg 90%; M.p: 109-110 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 12.01 (s, 1H), 9.42 (s, 1H), 8.38 (s, 1H), 8.10-7.86 (m, 2H), 7.88 (dd, *J* = 4.0, 7.5 Hz, 2H), 7.30 (t, = 8.0 Hz, 2H), 7.12 (dd, *J* = 8.0, 11.5 Hz, 2H), 4.75-4.71 (m, 1H), 2.40-2.36 (m, 2H), 1.81-1.72 (m, 1H), 1.40 (t, *J* = 3.5 Hz, 3H), 0.86 (s, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>): δ 175.5, 148.4, 144.6, 142.7, 141.4, 140.9, 139.3, 138.3, 130.7, 130.6, 128.9 (5C), 127.2,

44.1, 40.4, 29.4, 18.6; ESI MS: m/z, 361.2 [M+1] Anal. calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O.

**(E)-2-(4-Isobutylphenyl)-N'-((4-nitrothiophen-2-yl) methylene)propanehydrazide (5j)**

White solid; Yield: 155 mg 95%; M.p: 119-120 °C; IR (KBr): 3167, 3098, 2925, 2951, 2869, 1163, 1602, 1562, 1543, 1502, 1465, 1435, 1383, 1327, 1279, 1242, 1204, 1087, 1011, 944, cm<sup>-1</sup>; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.62 (s, 1H), 8.30 (s, 1H), 8.20-8.17 (m, 2H), 7.28-7.20 (m, 2H), 7.12-7.0 (m, 2H), 4.68-4.58 (m, 1H), 2.40-2.34 (m, 2H), 1.86-1.68 (m, 1H), 1.38 (d, *J* = 5.2 Hz, 3H), 1.82-1.76 (m, 6H); ESI MS: m/z, 360.1 [M+1] Anal. calcd. for C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S.

**(E)-2-(4-Isobutylphenyl)-N'-((5-nitrothiophen-2-yl) methylene)propanehydrazide (5k)**

White solid; Yield: 155 mg 95%; M.p: 135-136 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.82 (s, 1H), 8.45 (s, 1H), 8.07 (dd, *J* = 4.5, 6.5 Hz, 1H), 7.44 (dd, *J* = 4.5, 6.5 Hz, 1H), 7.22 (t, *J* = 8.5 Hz, 2H), 7.07 (t, *J* = 8.5 Hz, 2H), 4.50-4.46 (m, 1H), 2.40-2.34 (m, 2H), 1.80-1.73 (m, 1H), 1.35 (t, *J* = 3.5 Hz, 3H), 0.84-0.79 (m, 6H); <sup>13</sup>C NMR (100 Hz, DMSO-*d*<sub>6</sub>): δ 175.1, 150.6, 146.7, 140.1, 139.6, 138.7, 135.8, 130.5, 129.3, 128.9, 127.1, 44.1, 40.4, 29.5, 22.1, 18.3; ESI MS: m/z, 360.1 [M+1] Anal. calcd. for C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S.

**(E)-2-(4-Isobutylphenyl)-N'-((4-phenyl-4H-imidazol-2-yl) methylene)propanehydrazide (5l)**

White solid; Yield: 159 mg 94%; M.p: 138-139 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.54 (s, 1H), 8.33 (s, 1H), 7.94-7.79 (m, 2H), 7.77-7.73 (m, 5H), 7.71-7.06 (m, 4H), 4.66 (brs, 1H) 2.42-2.38 (m, 2H), 1.81-1.74 (m, 1H), 1.40 (t, *J* = 4.2 Hz, 3H), 0.86 (s, 6H); ESI MS: m/z, 375.2 [M+1] Anal. calcd. for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O.

**(E)-2-(4-Isobutylphenyl)-N'-((4-phenylpyridin-2-yl) methylene)propanehydrazide (5m)**

White solid; Yield: 166 mg 95%; M.p: 122-123 °C; <sup>1</sup>H NMR (500 Hz, DMSO-*d*<sub>6</sub>): δ 11.55 (s, 1H), 8.68 (s, 1H), 8.16-8.01 (m, 2H), 7.76 (d, *J* = 6.5 Hz, 2H), 7.97-7.90 (m, 2H), 7.89 (s, 1H), 7.11-7.07 (m, 2H), 7.28 (d, *J* = 6.5 Hz, 2H), 4.69-4.65 (m, 1H) 2.41 (d, *J* = 7.0 Hz, 2H), 1.81-1.77 (m, 1H), 1.39 (t, *J* = 6.0 Hz, 3H), 0.85 (d, *J* = 6.0 Hz, 6H); ESI MS: m/z, 386.3 [M+1] Anal. calcd. for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O.

**Antimicrobial bioassay**

The hydrazone derivatives **5a-m** was tested for antimicrobial activity by disc diffusion method.<sup>[11]</sup> The bacterial (24 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified nutrient agar, nutrient medium. The filter paper disks prepared by only DMSO (as a negative control) and with solution of 100 µg/mL concentrations of test compounds **5a-m** as well as standard compounds (Norfloxacin as positive control) were carefully placed over the spread cultures and incubated at 37 °C for 24 h.

After the incubation period, the plates were examined for the zone of inhibition. The diameter for the zones of inhibition was measured including the diameter of disk also. All determinations were made in triplicate for each of the compounds and the average value was taken. The antibacterial activity was evaluated against *E. coli* and *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria) using Norfloxacin (for bacteria) as the standard drugs.

## RESULTS AND DISCUSSION

### Chemistry

The synthesis of (*E*)-*N'*-(aromatic/ heteroaromatic)-2-(4-isobutylphenyl) propanehydrazides **5a-m** is given in **scheme** (1). Treatment of Ibuprofen (2-(4-isobutylphenyl) propanoic acid) **1** with ethanol in presence of catalytic conc; H<sub>2</sub>SO<sub>4</sub> resulted in the corresponding ethylester derivative ethyl 2-(4-isobutylphenyl) propanoate **2** in 72% yield. Reaction of ethylester **2** with hydrazine-hydrate in ethanol at reflux for 4h yielded 2-(4-isobutylphenyl) propanehydrazide **3**. Condensation of compound **3** with various aromatic and hetero aromatic aldehydes (**4**) in ethanol at reflux for 1h afforded hydrazones **5a-m**. The structures of these compounds were confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass and IR data. Moreover, all compounds were found to exist as a mixture of two rotameric forms in solution<sup>[12-14]</sup> e.g. antiperiplanar (ap) and synperiplanar (sp) as indicated by their <sup>1</sup>H NMR spectra. Two sets of signals were observed for all groups in the 1H NMR spectra of each compound indicating the possibility of

equilibrium and interconversion between rotamers (and/or configurational isomers) in solution. As an example, the proton NMR of (*E*)-*N'*-(3,4,5-trimethoxybenzylidene)-2-(4-isobutylphenyl) propanehydrazide **5f**, is exemplified here, the proton signal of para-substituent pattern of 4-(isobutyl phenyl)propanehydrazide appeared at 7.24 ppm and 7.09 ppm, while the proton signal of 3,4,5-trimethoxy phenyl ring resonated at 6.95ppm as singlet. The characteristic signals at 11.44 ppm and 8.12 ppm corresponds to –CONH- and –N=CH- groups respectively. The aliphatic protons of hydrazone **5f** such as isobutyl, methylene, methine and methoxylated protons appeared in the expected region.

### Antibacterial activity

The results of the antibacterial activity of hydrazones **5a-m** are presented in **table 1**. Compounds **5h**, **5i**, **5j**, **5k**, **5l** and **5m** exhibited good antibacterial activity (zone of inhibition: 18-25 mm, at concentration: 100 µg/mL) compared to the standard drug Norfloxacin (zone of inhibition: 21-27 mm, at concentration: 100 µg/mL) against both the gram positive and gram negative bacteria. Compounds **5b**, **5c** and **5d** showed moderate activity and compounds **5e**, **5f** and **5g** displayed weak activity while the compound **5a** showed no activity. From the results, it is clear that hydrazone derivatives bearing heterocyclic ring substituent's were found to exhibit significant antibacterial activity. Therefore, these compounds would be enhanced to be used in drug development to fight bacterial infections.

**Table 1: Antibacterial and Antifungal Activities of compounds 5a-m.**

Compound No	Gram negative bacteria		Gram positive bacteria	
	<i>E.coli</i> MTCC 443	<i>P.aeruginosa</i> MTCC 424	<i>S.aureus</i> MTCC 96	<i>S.pyogenes</i> MTCC 442
	Zone of inhibition			
<b>5a</b>	-	-	-	-
<b>5b</b>	20	16	19	14
<b>5c</b>	18	16	19	16
<b>5d</b>	16	18	17	15
<b>5e</b>	14	10	11	9
<b>5f</b>	13	11	11	8
<b>5g</b>	14	11	12	8
<b>5h</b>	23	22	24	20
<b>5i</b>	24	22	25	19
<b>5j</b>	21	19	22	16
<b>5k</b>	21	18	22	15
<b>5l</b>	23	21	24	18
<b>5m</b>	22	22	23	20
Norfloxacin	27	23	26	21

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### CONCLUSION

The newly synthesized hydrazones derivatives **5a-m** of Ibuprofen was characterized by spectral data and evaluated for antibacterial studies. In general, hydrazones bearing R = heterocyclic rings exhibited good antibacterial activity against the bacterial strains

viz., *P. aeruginosa* (Gram negative bacteria), *S. aureus* and *S. pyogenes* (Gram positive bacteria).

## REFERENCES

1. Sreeja PB, Kurup MRP, Kishore A and Jasmin C. Spectral characterization, X-ray structure and biological investigations of copper(II) ternary complexes of 2-hydroxyacetophenone 4-hydroxybenzoic acid hydrazone and heterocyclic bases. *Polyhedron.*, 2004; 23: 575.
2. Vora JJ, Vasava SB, Parmar KC, Chauhan SK and Sharma SS. Synthesis, Spectral and Microbial Studies of Some Novel Schiff Base Derivatives of 4-Methylpyridin-2-amine. *E-Journal of Chemistry*, 2009; 6(4): 1205-1210.
3. Rollas S and Kucukguzel SG. Biological Activities of Hydrazone Derivatives. *Molecules*, 2004; 12: 1910.
4. Tenover FC, and McDonald LC, Vancomycin-resistant staphylococci and enterococci: epidemiology and control. *Curr. Opin. Infect. Dis.*, 2005; 18: 300.
5. Pfeltz RF, and Wilkinson BJ. The escalating challenge of vancomycin resistance in *Staphylococcus aureus*. *Curr. Drug Targets: Infect. Disord*, 2004; 4: 273.
6. Roberts MC. Distribution of Macrolide, Lincosamide, Streptogramin, Ketolide and Oxazolidinone (MLSKO) Resistance Genes in Gram-negative Bacteria. *Curr. Drug Targets: Infect. Disord.*, 2004; 4: 207.
7. Dessen A, Di Guilmi AM, Vernet T and Dideberg O, Molecular mechanisms of antibiotic resistance in gram-positive pathogens. *Curr. Drug Targets: Infect. Disord*, 2001; 1: 63.
8. Muroi H, Nihei K, Tsujimoto K, and Kubo I. Synergistic effects of anacardic acids and methicillin against methicillin resistant *Staphylococcus aureus*. *Bioorg. Med. Chem.*, 2004; 12: 583.
9. Bradbury F. How important is the role of the physician in the correct use of a drug? An observational cohort study in general practice. *International Journal of Clinical Practice*, 2004; 144: 27.
10. Tripathi KD. Non-steroidal anti-inflammatory drugs and anti-pyretic analgesics. *Essentials of medical pharmacology*. 5th Edition, Jaypee Brothers, New Delhi, 2003.
11. Bushra R, and Aslam N. An Overview of Clinical Pharmacology of Ibuprofen. *Oman Medical Journal*, 2010; 25: 155.
12. Biljana RD, Niko SR, Vidoslav SD, Vukicević RD and Palić RM, Synthesis and Antimicrobial Activity of New 4-Heteroaryl amino Coumarin Derivatives Containing Nitrogen and Sulfur as Heteroatoms. *Molecules*, 2010; 15: 2246.
13. Palla G, Predieri, G and Domiano P. Conformational behaviour and *E/Z* isomerization of *N*-acyl and *N*-aroylhydrazones. *Tetrahedron*, 1986; 42: 3649.
14. Sarbani P. Naproxen and ibuprofen based acyl hydrazone derivatives: Synthesis, structure analysis and cytotoxicity studies. *J. Chem. Pharm. Res.*, 2010; 2: 393.
15. Palmer RB and Andersen NH. Synthesis and X-ray Crystal Structure of 1,4-Dihydro-2,6-dimethyl-4-(2'-isopropylphenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester: A Nifedipine Analogue. *Bioorg. Med. Chem. Lett.*, 1996; 6: 2173.