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Synthesis and Antibacterial Activity of Novel (E)-N'-((2-(Naphthalen-8-yl) phenyl)methylene)Benzohydrazide Derivatives

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ABSTRACT

The present paper reports the synthesis and antibacterial activity of ten new (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide derivatives ***6a-j*** *from commercially available naphthalene-1-yl-1-boronic acid as starting material. The benzohydrazides* ***6a-j*** *have been screened against four bacterial strains such Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus pyogenes. The results of the antibacterial activity data indicated that within the (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide* ***6a – j****, compounds incorporated with the substituent's such as 4-F, 4-OH, 3,4,5-trimethoxy, 3-NO_2 and 4-SO_2-CH_3 exhibited excellent antibacterial activity while the compounds having the substituent's H, 2-Br, 4-Br, 2-I and 4-Cl displayed moderate antibacterial activity.*

Keywords: Antibacterial activity, Formylation, Suzuki reaction, Naphthalene-1-yl-boronic acid.

INTRODUCTION

The design and synthesis of new antibacterial molecules has been of immense interest in recent year. A range of strategies are currently being engaged to develop new antibiotics and to precede the effectiveness of predictable antimicrobial compounds. The additional striking approach for the growth of antibacterial agents is to explore the novel compounds that target bacterial membranes [1, 2]. Several naphthalene containing drugs are available, such as nafacillin, naftifine, tolnaftate, terbinafine, etc. which play vital role in the control of microbial infection [3]. Also, Naphthalene derivatives display biological significance such as antioxidant activity [4], antimicrobial activity [5], antifungal activity [6], anti-inflammatory [7], analgesic activity [8], anticonvulsant and anti-tubular activity [9-15]. It has also been reported that compounds containing hydrazide-hydrazone moiety possess good analgesic, anti-inflammatory [16-21] and antimicrobial activities [22-25]. In addition, hydrazone moiety play an important key role in heterocyclic chemistry [26-32] and some evidences showed the hydrazone moiety that present in the anti-inflammatory drug structure of COX is behind its inhibition character [33]. Encouraged by these reported activities and with the aim of searching for new, broad spectrum and more potent antimicrobial compounds which can improve the current chemotherapeutic treatments, we have synthesized, ten new (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide derivatives and evaluated for antibacterial activity studies.

MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded in Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal standard and the signals were reported as s (singlet), d (doublet), dd (doblet of doblet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer.

Synthesis of 1-(2-bromophenyl)naphthalene 3: To a mixture of 2-iodo-bromo benzene (1.0 g, 5.81 mmol), 2M sodium carbonate (0.56 g, 5.32 mmol), palladium tetrakis (0.01 mmol) in 50% toluene : water (10 mL) was added naphthalene boronic acid (0.61g, 8.71 mmol) and stirred at reflux temperature for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with ethylacetate and evaporated under reduced pressure to obtain the crude compound **3,** which was used as such for the next step.

Synthesis of 2-(napthalen-8-yl)benzaldehyde 4: To a mixture of compound **3** (1g, 1.1 mmol) , 1.6M BuLi (0.226 g, 4.23 mmol) in THF (10 mL) was added N,N-Dimethylformamide (0.404 g, 5.28 mmol) and stirred at -78^{0}C for 2h. The reaction mixture was warmed to room temperature and extracted with ethylacetate and evaporated under reduced pressure to obtain the crude compound **4,** which was purified by column chromatography (silica gel: 60 – 120 mesh, eluent: 5% ethylacetate / petether) to afford compound **4** as a pale yellow solid. Yield: 65%; m.p 109- 110^0 C. 1H NMR (400 MHz, CDCl3): δ 9.6 (s,1H), 8.16 (d, *J* = 6.8 Hz, 1H), 7.98 (d, *J* = 6.6 Hz, 2 H), 7.72 (d, J= 6.6 Hz, 1H), 7.4-7.6 (m, 7H). ESI-MS: m/z (rel.abund.%) 233.0 (M+,100).

Experimental procedure for synthesis of Benzohydrazide derivatives 5 (a – j) : To a stirred solution of benzoic acids (6.42 mmol) in ethanol (3 mL) was added catalytic qty of conc.H_2SO_4 and heated to reflux for 6 – 10 h. The reaction mixture was diluted with ethylacetate followed by water. The organic layer was washed with saturated $NaHCO_3$ followed by water and brine solution. The organic layer was dried over sodium sulphate, filtered and evaporated to obtain respective ethyl benzoates derivatives.To a stirred solution of ethyl benzoates (3 mmol) derivatives in ethanol was added hydrazine-hydrate (5.44 mmol) and refluxed for 6 – 12 h. The reaction mixture was diluted with ethylacetate followed by water. The organic layer was dried over sodium sulphate, filtered and evaporated to obtain respective benzohydrazide derivatives **5** (a-j). The yields of the products varied from 75 – 88%.

General experimental procedure for the preparation of novel (E)-N'-((2-(naphthalen-8-yl) phenyl) methylene)benzohydrazide (6a-6j): To a stirred solution of compound **4** (100 mg, 0.430 mmol) in ethanol was added corresponding benzohydrazides (1.0 mmol) and refluxed for **5** h. The reaction medium was poured into water and extracted with ethyl acetate. The organic layer was washed with water followed by brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure, to obtain the pure compounds. Yields of the products varied between 70 to 92%.

Synthesis of (E)-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6a) : Yield: 83%; m.p: 135-136 ^{o}C; IR (KBr): υ_{max} 3455.87, 3189.39, 3060.01, 2848.67, 1721.22, 1651.82, 1556.49, 1369.48, 1303.35, 1289.73, 1152.63, 1074.94, 1065.69, 964.86, 917.81, 813.23, 783.47, 705.88, 680.60 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.61 (s, 1H), 8.2 (brd,1H), 8.4 (d, *J* = 8.8 Hz, 2H), 7.96 (m, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.3-7.6 (m, 10H); ESI-MS: m/z, 351.15 (M+1).

Synthesis of (E)-2-bromo-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6b) : Yield: 88%; m.p: 211-213 ^{o}C; IR (KBr): υ_{max} 3434.05, 3184.41, 3052.10, 2848.37, 1655.33, 1591.87, 1556.39, 1355.60, 1295.62, 1250.88, 1153.03, 1067.62, 1046.06, 919.82, 813.44, 784.26, 763.39, 745.58 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.61 (s, 1H), 8.2 (d, J= 8.2 Hz,1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.76 (s, *1H), 7.7 (d, *J* = 8.2 Hz, *1H), 7.54-7.64 (m, 5H), 7.44 (m, 2H), 7.22-7.4 (m, 6H); ESI-MS: m/z, 431.03 (M+2).

Synthesis of (E)-2-iodo-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6c) : Yield: 78%; m.p: 211-202 ^{o}C; IR (KBr): υ_{max} 3437.11, 3179.89, 3043.43, 2923.01, 2852.00, 1656.23, 1588.08, 1555.98, 1353.61, 1292.57, 1250.83, 1151.50, 1066.05, 958.86, 917.65, 782.41, 743.86, 722.55 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.61 (s, 1H), 8.2 (brd,1H), 8.0 (d, *J* = 8.4 Hz, 2H), 8.05 (brd,*1H), 7.9 (d, *J* = 8.4 Hz,*1H), 7.81 (d, *J* = 8.2 Hz,1H), 7.77 (s, 1H), 7.5 (m, 6H), 7.44-7 (m, 3H), 7.24 (m, *7H), 7.12 (m, 2H); ESI-MS: m/z, 477.11 (M+1).

Synthesis of (E)-4-bromo-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6d) : Yield: 89%; m.p: 266-269 ^{o}C; IR (KBr): υ_{max} 3467.23, 3191.89, 3024.10, 3053.59, 2856.77, 1645.48, 1563.27, 1592.58, 1478.70, 1393.19, 1355.78, 1311.33, 1289.02, 1273.19, 1146.48, 1064.97, 1010.41, 914.88, 840.40, 801.49, 779.73, 764.20, 657.65, 641.49, 620.62 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.61 (s, 1H), 8.2 (brd,1H), 8.4 (d, *J* = 8.8 Hz, 2H), 7.95 (m, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.62 (m, 3H), 7.56 (m, 3H), 7.46 (t, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 2H) ; ESI-MS: m/z, 431.03 (M+2).

Synthesis of (E)-4-chloro-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6e) : Yield: 91%; m.p: 269-272 ^{o}C; IR (KBr): υ_{max} 3435.75, 3190.91, 3053.91, 3024.28, 2856.76, 1645.40, 1597.46, 1568.22, 1480.0, 1489.24, 1355.50, 1301.50, 1312.97, 1288.44, 1277.53, 1148.08, 1066.75, 1091.67, 1014.22, 916.73, 844.16, 801.56, 764.27, 779.98, 664.17, 535.25 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.6 (s, 1H), 8.2 (brd,1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.95 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.5 (m, 3H), 7.55 (m, 3H), 7.4 (d, *J* = 8.2 Hz, 1H), 7.3 (t, *J* = 8.8 Hz, 2H); ESI-MS: m/z, 385.10 (M+1).

Synthesis of (E)-4-hydroxy-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6f) : Yield: 87%; m.p: 219-218 ^{o}C; IR (KBr): υ_{max} 3350.83, 3258.75, 3052.07, 1668.19, 1609.14, 1582.20, 1532.37, 1510.02, 1479.39, 1444.19, 1353.61, 1266.75, 1231.34, 1183.50, 847.41, 779.04, 766.87, 713.43, 621.62, 514.53 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.4 (s, 1H), 10.0 (s, 1H), 8.16 (brd,1H), 8.04 (d, *J* = 8.0 Hz, 2H), 7.92 (br, 1H), 7.62 (m, 3H), 7.52 (m, 3H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 6.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H); ESI-MS: m/z, 367.0 (M+1).

Synthesis of (E)- N'-((2-(napthalene-8-yl)phenyl)methylene)-3-nitrobenzohydrazide (6g) : Yield: 90%; m.p: 210-213 ^{o}C; IR (KBr): υ_{max} 3436.93, 3229.05, 3056.0, 2867.76, 2745.04, 1694.70, 1645.95, 1621.04, 1594.35, 1526.85, 1381.92, 1346.31, 1326.48, 1160.24, 1061.74, 949.62, 962.91, 801.29, 763.48, 777.14, 713.30, 575.86 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.85 (s, 1H), 8.55 (m,1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.98 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.45-7.65 (m, 6H), 7.35 (m, 2H); ESI-MS: m/z, 396.15 (M+1).

Synthesis of (E)-4-(methylsulfonyl)-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6h) : Yield: 90%; m.p: 215-214 ^{o}C; IR (KBr): υ_{max} 3450.15, 3195.25, 3034.20, 2925.64, 1648.14, 1609.74, 1566.84, 1311.99, 1299.65, 1154.11, 1138.44, 10888.62, 1062.15, 956.28, 857.15, 800.62, 779.26, 743.71, 559.17 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.6 (s, 1H), 8.24 (brd,1H), 8.1 (d, *J* = 8.4 Hz, 2H), 7.98 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.5 (m, 3H), 7.45 (m, 3H), 7.4 (d, *J* = 8.2 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 2H), 2.88 (s, 3H);ESI-MS: m/z, 428.9 (M+1).

Synthesis of (E)-4-fluoro-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6i) : Yield: 78%; m.p: 198-199 ^{o}C; IR (KBr): υ_{max} 3233.3, 3054.38, 1642.46, 1606.5, 1574.46, 1508.16, 1363.10,

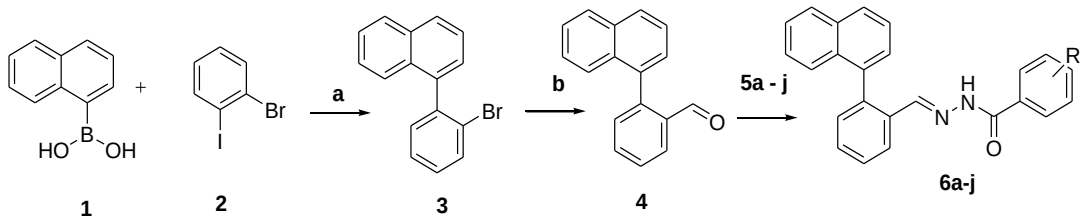
1320.64, 1288.41, 1234.40, 1165.41, 1064.94, 918.12, 848.25, 779.27, 757.36, 612.21cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.6 (s, 1H), 8.22 (brd,1H), 8.4 (d, *J* = 8.2 Hz, 2H), 7.94 (m, 1H), 7.82 (t, *J* = 8.2 Hz, 2H), 7.64 (t, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 8.2 Hz, 1H), 7.42 (d, *J* = 6.8 Hz, 1H), 7.32 (m, 2H), 7.22 (t, *J* = 8.0 Hz, 2H); ESI-MS: m/z, 369.0 (M+1).

Synthesis of (E)-3,4,5-trimethoxy-N'-((2-napthalene-8-yl)phenyl)methylene)benzohydrazide (6j) : Yield: 88%; m.p: 186-187 ^{o}C; IR (KBr): υ_{max} 3437.90, 3220.22, 3054.78, 2999.50, 2932.79, 2835.48, 1636.35, 1581.91, 1504.07, 1461.93, 1329.80, 1237.64, 1129.88, 1005.20, 862.01, 800.26, 782.46, 649.51 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.6 (s, 1H), 8.22 (brd,1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.94 (m, 1H), 7.54 (m, 4H), 7.42-7.46 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 2H), 3.88 (s, 6H), 3.7 (s, 3H); ESI-MS: m/z, 441.25 (M+1).

In Vitro Antibacterial Assay: The newly synthesized (E)-N'-((2-(naphthalen-8-yl) phenyl) methyl ene) benzohydrazides **6a-j,**were dissolved in dimethylsulphoxide at 25 µg mL^{-1} concentration and tested against i) *Escherichia coli* (MTCC 443), *(ii) Pseudomonas aeruginosa* (MTCC 424) (Gram negative strains) and (iii) *Staphylococcus aureus* (MTCC 96) strains *iv) Streptococcus pyogenes* (MTCC 442) (Gram positive strains) using agar well diffusion method according to the literature protocol [34-36]. The composition of nutrient agar medium was Bactotryptone (10 g), Yeast extract (5 g), NaCl (10 g), final pH 7.4. After 18 h the exponentially growing cultures of the four bacteria in nutrient broth at 37 ^{o}C were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell/ml. The plates were set at room temperature and later dried at 37 ^{o}C for 20h. Paper discs (6mm, punched from Whatman no 41 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. The plates were incubated at 37 ^{o}C in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicates.

RESULTS AND DISCUSSION

The synthesis of (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazides **6a-j** described is outline in **Scheme 1**. The suzuki reaction of naphthalene-1-yl boronic acid **(1)** with 2-iodobromobenzene (**2)** in presence of catalytic qty; of $Pd(PPh_3)_4$, 2M aqueous sodium carbonate in toluene and water at reflux temperature for 12 h resulted in the formation of 1-(2-bromophenyl)napthalene **3**. The formylation reaction of 1-(2-bromophenyl)napthalene **3** was carried out using N,N dimethyl formamide in presence of n-butyl lithium in anhydrous THF at -78 ^{o}C (to room temperature) for 2h to produce 2-(napthalen-8-yl)benzaldehyde **4**. The napthalen carboxaldehyde **4 was** further reacted with corresponding benzo hydra zide derivatives **5a-j** in ethanol to afford (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide **6a–j** in 78 -90% yield (**Scheme 1**). The structures of the newly synthesized compounds were confirmed by various analytical methods such as ^{1}H NMR, Mass and IR data. As a representative example, the ^{1} H NMR spectra of the compound **6d** is as follows, the broad and sharp singlets at 8.2 and 11.6 ppm corresponds to the protons representing to -N=C*H*- and -N*H*-N=C groups respectively. All the other aromatic protons were observed at expected regions. The ^{1}H NMR data for the derivatives **6a-j** are in agreement with the assigned structures. The mass spectra of compounds showed (M+1) peaks, in agreement with their molecular formula.



6a. R =H; 6b. R = 2-Br; 6c. R = 2-I; 6d. R = 4-Br; 6e. R = 4-Cl; 6f. R= 4-OH, 6g. R = 3-NO_2; 6h. R = 4-$MeSO_2$; 6i. R = 4-F; 6j. R = 3, 4 , 5-OMe

Reagents and Conditions: a) Pd $(PPh_3)_4$, aqueous; 2M Na_2CO_3, Toluene:water, reflux, 12 h; b) DMF, BuLi, THF, -78 ^oC-rt, 2 h; c) Benzohydrazides **5a-j**, EtOH, reflux, 2 h.

Scheme-1: Synthesis (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide 6a-j

APPLICATIONS

The results of the antibacterial activity data of the newly synthesized (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazides **6a–j**, is presented in **table 1.** Within the series of benzohydrazides 6a-j, it is observed that compounds **6f, 6g, 6h, 6i** and **6j** exhibited excellent antibacterial activity while the compounds **6a-e** displayed moderate antibacterial activity against all the tested bacterial strains *viz.*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. It is noteworthy to observe that within the (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazides **6a – j**, compounds incorporated with the substituent's such as 4-F, 4-OH, 3,4,5-trimethoxy, 3-NO_2 and 4-SO_2CH_3 exhibited excellent antibacterial activity while the compounds having the substituent's H, 2-Br, 4-Br, 2-I and 4-Cl displayed moderate antibacterial activity. From the above antibacterial data it can be suggested that, by further hit and trials on modification of R in the (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazides **6a-j** derivatives may lead to a promising antibacterial agent.

Table-1: Antibacterial Activity of Compounds **6a-j** (Concentration Used 25 µg mL^{-1} of DMSO)

Compound No.	*Gram negative*		*Gram positive*	
	E.coli ***MTCC 443***	*P.aeruginosa* ***MTCC 424***	*S.aureus* ***MTCC 96***	*S.pyogenes* ***MTCC 442***
	Zones of Inhibition of compounds 6a –6j in mm			
6a	17	11	17	11
6b	18	12	17	11
6c	17	15	19	16
6d	16	14	19	15
6e	18	12	18	13
6f	26	21	27	20
6g	27	20	26	20
6h	28	23	28	23
6i	27	23	26	23
6j	26	22	25	23
Standard Drug Norfloxacin (25 µg/mL of DMSO)	25	19	25	19

CONCLUSIONS

In conclusion, the present paper describes the synthesis and antibacterial activity of ten new (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazides from commercially available naphthalene-1-yl - boronic acid as staring material in three steps and was screened against four bacterial strains such *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*. It is observed that within the (E)-N'-((2-(naphthalen-8-yl)phenyl)methylene)benzohydrazide **6a – 6j**, compounds incorporated with the substituent's such as 4-F, 4-OH, 3,4,5-trimethoxy, 3-NO_2 and 4-SO_2-CH_3 exhibited excellent antibacterial activity while the compounds having the substituent's H, 2-Br, 4-Br, 2-I and 4-Cl displayed moderate antibacterial activity.

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