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Synthesis and Antibacterial Activity of 4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl-methanone Derivatives and its Intermediates

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Encouraged by the interesting biological activities associated with benzo[b]furan derivatives, we report here the synthesis, spectroscopic identification and antibacterial activity of benzo[b]furan derivatives (**6a-6g**) prepared from commercially available, 3,5-dimethoxyphenol and 1-ethynyl-4-methoxybenzene. The synthesized targets were screened for their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococus pyogenes*, while using norfloxacin, as the standard drug. In general, it is observed that benzo[b]furan derivatives (**6a**, **6b**, **6c**) having R = 2,4-dimethoxy phenyl, 2,4,6-trimethoxy phenyl and 3,4,5-trimethoxy phenyl rings, respectively displayed excellent activity against these microbial species while compound **5** (having benzo[b]furan motif) showed good activity and the compound **2** (having -OH group) and compound **4** (having acetate group) exhibited moderate antibacterial activity.

Keywords: Antibacterial activity, Benzo[b]furan, 3,5-Dimethoxy phenol, Norfloxacin.

INTRODUCTION

The benzo[b]furans are significant heterocyclic compounds, which not only act as key structural subunits in naturally occurring compounds that show remarkable biological activities but also signify useful building blocks in the synthesis of natural products[1-4]. Numerous synthetically challenging and medicinally important chemicals contain benzo[b]furan moiety as structural units[5]. Some of the properties of pharmaceutically active molecules, which contains benzo[b]furans are antifungal properties[6,7], inhibition of 5-lipoxygenase (5-LO)[8], antitumor properties[9] and therefore these type of compounds can be used for treatment of type-2 diabetes, cardiovascular disease, cancer, dementia, migraines and anxiety[10,11]. Benzo[b]-furan-based molecules have also been disclosed as promising drugs against Parkinson's[12] and Alzheimer's disease, the inhibitors of β-amyloid (Ab) aggregation[13,14] and cyclooxy-genase-2 (COX-2)[15]. The present paper describes the synthesis, spectroscopic identification and antibacterial activity of benzo[b]furan derivatives (**6a-6g**) prepared from commercially available 3,5-dimethoxyphenol and 1-ethynyl-4-methoxy-benzene (**Scheme-I**). The synthesized targets were screened for their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococus pyogene*s, while using norfloxacin, as the standard drug.

EXPERIMENTAL

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 under UV light. Merck silica gel (100-200 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point 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 tetrame-thylsilane (TMS) with reference to internal standard 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. All the aromatic acid chlorides used for the preparation of **6a-6g** were purchased from commercial sources.

Synthesis of 2-iodo-3,5-dimethoxyphenol (2): To a stirred solution of compound **1** (5 g, 32.46 mmol) in acetonitrile (50 mL) was added ceric ammonium nitrate (1.77 g, 3.24 mmol) followed by addition of iodine (8.21 g, 32.46 mmol) in portion wise. The reaction mixture was stirred at room temperature for 7 h. After completion of the reaction, the reaction contents

were quenched with saturated sodium thiosulphate, extracted with EtOAc (2 × 60 mL). The organic layers was dried over anhydrous Na_2SO_4, filtered and evaporated under pressure. The crude compound was purified by column chromatography using 100-200 silica gel and eluted with 3 % EtOAc/pet ether to afford compound **2** as pale yellow solid; Yield: 3 g, 33 %; m.p. 76-77 °C. IR (KBr, ν_{max}, cm^{-1}): 3420, 3364, 3097, 2935, 2841, 1584, 1462, 1428, 1343, 1320, 1209, 1152, 1088, 1031, 976, 927, 819, 659, 573, 526, 469; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 6.36 (s, 1H), 6.12 (s, 1H), 3.78 (s, 3H), 3.82 (s, 3H); ESI-MS: *m/z*, 281.06 (M + 1).

Synthesis of 2-iodo-3,5-dimethoxyphenyl acetate (3): To a solution of compound **2** (4 g, 14.28 mmol) in dichloromethane (40 mL) was added pyridine (2.22 g, 28.57 mmol) followed by drop wise addition of acetic anhydride (2.91 g, 28.57 mmol) at 0 °C. The reaction mixture was stirred for 2 h at ambient temperature and poured in to dichloromethane, washed with 5 % $NaHCO_3$ and brine solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The purification was carried out by flash chromatography using over 100-200 silica gel and eluted with 9 % EtOAc /Pet ether to afford compound **3**. White solid; Yield: 2.3 g, 50 %; m.p. 126-128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (s, 2H), 3.78 (s, 3H), 3.84 (s, 3H), 2.38 (s, 3H); ESI-MS: *m/z*, 323.06 (M + 1).

Synthesis of 3,5-dimethoxy-2-(2-(4-methoxyphenyl)-ethynyl)phenyl acetate 4: To a solution of compound **3** (700 mg, 2.17 mmol) in DMF (5 mL) was added 1-ethynyl-4-methoxybenzene (370 mg, 2.79 mmol), triethylamine (440 mg, 4.31 mmol) followed by CuI (21 mg, 0.1 mmol) and $Pd(PPh_3)_2Cl_2$ (30 mg, 0.043 mmol). The reaction mixture was heated at 100 °C for 5 h and then slowly warmed to an ambient temperature, diluted with water, extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The purification was carried out by flash chromatography over 100-200 silica gel and eluted with 16 % EtOAc/pet-ether to afford compound **4** as an off white solid; Yield: 0.5 g, 71 %; m.p: 124-126 °C. ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.8 Hz, 2H), 6.82 (d, *J* = 7.8 Hz, 2H), 6.38 (s, 1H), 6.32 (s, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 2.38 (s, 3H); ESI-MS: *m/z*, 327.3 (M + 1).

Synthesis of 4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran (5): To a solution of compound **4** (500 mg, 1.53 mmol) in methanol (7 mL) was added potassium carbonate (530 mg, 3.83 mmol) and and heated to 60 °C for 16 h. The excess methanol was evaporated under reduced pressure, diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The purification was performed by flash chromatography over 100-200 silica gel and eluted with 20 % EtOAc/pet ether to afford compound **5** as an off white solid; Yield: 0.37 g, 86 %; m.p. 165-167. IR (KBr, ν_{max}, cm^{-1}) 3424, 2932, 2834, 1612, 1499, 1456, 1418, 1315, 1256, 1211, 1140, 1104, 1030, 886, 836, 791, 618, 563, 512; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.84 (s, 1H), 6.70 (s, 1H), 6.30 (s, 3H), 3.88 (s, 3H), 3.82 (s, 6H); ^{13}C NMR: δ 159.3, 158.7, 156.2, 153.7, 153.2, 125.6, 123.6, 114.1, 113.3, 97.0, 94.1, 88.2; ESI-MS: *m/z*, 285.17 (M + 1).

General procedures for preparation of benzoyl chloride (a-g): To a stirred solution of benzoic acid in dichloromethane (DCM) was added oxalyl chloride at 0 °C and stirred for 3-4 h at an ambient temperature and then the reaction mixture was evaporated under pressure to obtain the corresponding benzoyl chloride which was used in the next step without further purification.

General experimental procedure for the synthesis of benzo[b]furan derivatives (6a-6g): To a solution of compound **5** (50 mg, 0.17 mmol) in dichloromethane (2 mL) was added benzoyl chloride (a-g) (1.2 eq) followed by $SnCl_4$ (1.0 eq) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction contents were quenched with ice and stirred for 1 h, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The purification was performed by flash chromatography over 100-200 silica gel and eluted with 27 % EtOAc/pet ether to afford compound **6a-6g**.

(4,6-Dimethoxy-2-(4-methoxyphenyl)-benzofuran-3-yl)(2,4-dimethoxyphenyl)methanone (6a): Off white solid; m.p.: 136-138 °C; IR (KBr, ν_{max}, cm^{-1}): 2940, 2839, 1606, 1503, 1456, 1402, 1302, 1252, 1216, 1169, 1107, 1028, 983, 933, 834, 790, 640, 578, 521; ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (d, *J* = 6.8 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 6.88 (m, 3H), 6.58 (d, *J* = 6.8 Hz, 1H), 6.42 (s, 2H), 6.38 (s, 1H), 4.02 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.60 (s, 3H); ^{13}C NMR: 163.9, 160.8, 159.4, 157.3, 154.5, 154.3, 154.1, 133.5, 125.7, 123.7, 123.1, 114.0, 113.6, 109.8, 104.5, 98.5, 96.1, 91.2 (2C), 57.3, 55.4, 55.2 (2C); ESI-MS: *m/z*, 449.3 (M + 1).

(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(2,4,6-trimethoxyphenyl)methanone (6b): ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 6.8 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 6.88 (m, 3H), 6.58 (d, *J* = 6.8 Hz, 1H), 6.42 (s, 2H), 6.38 (s, 1H), 6.26 (s, 2H), 4.02 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.60 (s, 3H); ESI-MS: *m/z*, 479.2 (M + 1).

(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(3,4,5-trimethoxyphenyl)methanone (6c): ^{1}H NMR (400 MHz, $CDCl_3$): 7.74 (d, *J* = 6.8 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 2H), 6.88 (m, 3H), 6.58 (d, *J* = 6.8 Hz, 1H), 6.42 (s, 2H), 6.38 (s, 1H), 6.24 (s, 2H), 4.02 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.60 (s, 3H); ESI-MS: *m/z*, 479.2 (M + 1).

(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(2-methoxyphenyl)methanone (6d): Off white solid; m.p.: 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.74 (d, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 6.82 (m, 3H), 6.50 (d, *J* = 6.8 Hz, 1H), 6.40 (s, 2H), 6.32 (s, 2H), 4.02 (s, 3H), 3.82 (s, 3H), 3.78 (s, 6H), 3.60 (s, 6H); ESI-MS: *m/z*, 553.4 (M + 1).

(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(4-methoxyphenyl)methanone (6e): Off white solid; m.p.: 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.65-7.06 (m, 2H), 7.45-7.42 (m, 2H), 7.08-7.02 (m, 1H), 6.90 (d, *J* = 6.8 Hz, 2H), 6.75 (d, *J* = 6.8 Hz, 2H), 6.25 (s, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H); ESI-MS: *m/z*, 553.4 (M + 1).

(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(4-fluorophenyl)methanone (6f): Pale yellow solid; m.p.: 108-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.13-8.06 (m, 1H), 7.93-7.89 (m, 2H), 7.50 (d, *J* = 6.8 Hz, 2H), 7.17-7.07 (m,

2H), 6.88 (m, 2H), 6.40 (s, 1H), 4.03 (s, 3H), 3.82 (s, 6H), 3.60 (s, 6H); ESI-MS: *m/z*, 407.2 (M + 1).

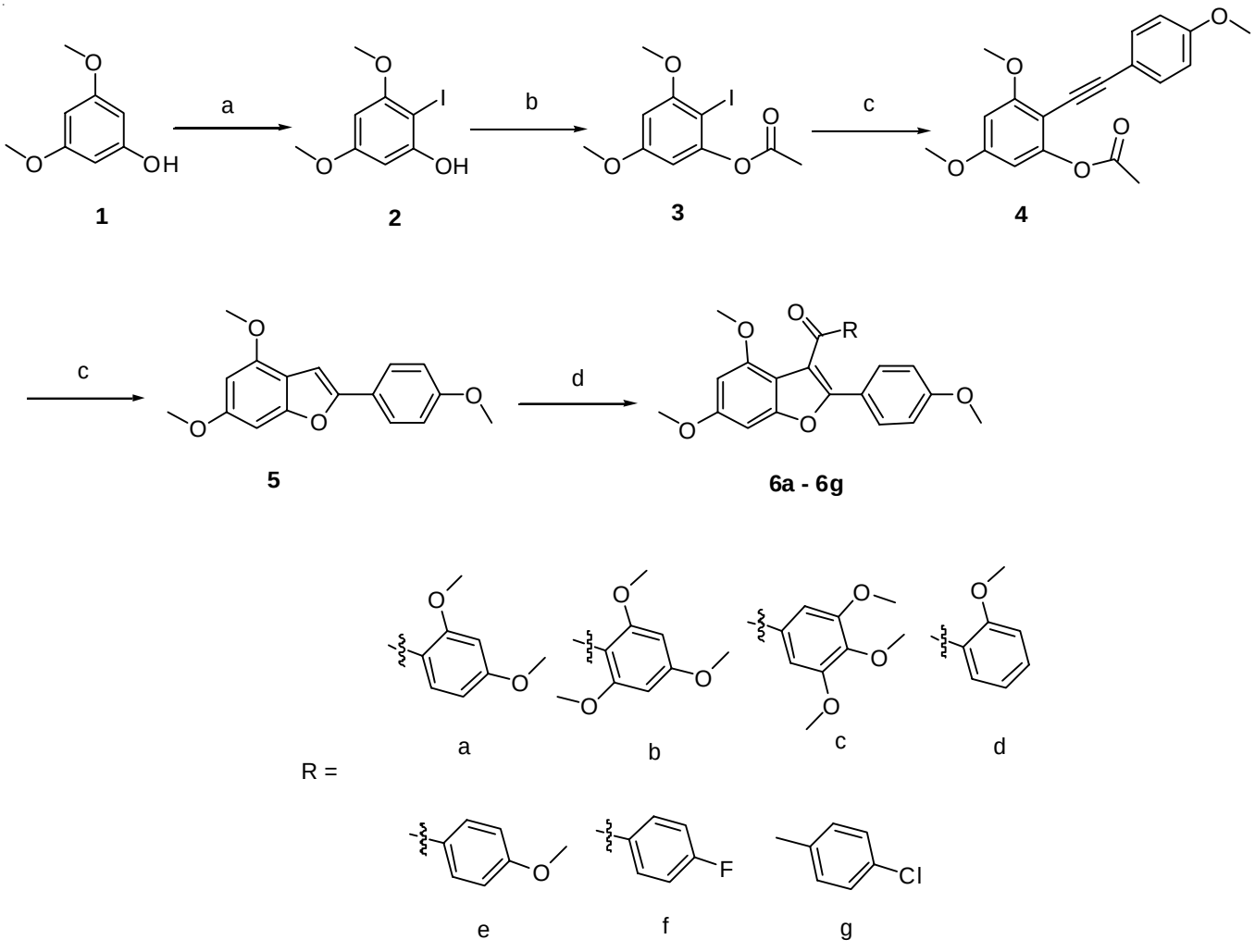
(4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)(4-chlorophenyl)methanone (6g): Pale yellow solid; m.p.: 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.03-8.00 (m, 1H), 7.90-7.86 (m, 2H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.22-7.18 (m, 2H), 6.88 (m, 2H), 6.40 (s, 1H), 4.03 (s, 3H), 3.82 (s, 6H), 3.60 (s, 6H); ESI-MS: *m/z*, 423.2 (M + 1).

Biological assay

All the synthesized new benzo[b]furan derivatives and its intermediates was dissolved in dimethyl sulphoxide at 25 µg/mL concentration and were tested against two Gram-negative strains *viz*., *Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC424) and two Gram positive strains *viz*., *Staphylococcus aureus* (MTCC96) and *Streptococcus pyogenes* (MTCC442) using agar well diffusion method according to the literature protocol[16-18]. The composition of nutrient agar medium was yeast extract (5 g), NaCl (10 g), bactotryptone (10 g), final pH 7.4. After 18 h, the exponentially growing cultures of the four bacteria in nutrient broth at 37 °C were diluted in sterile broth. From each of these diluted cultures, 1 mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1×10^6 cell/mL. The plates were set at room temperature and later dried at 37 °C for 20 h. Paper discs (6 mm, punched from Whatmann No. 1 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 °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

Benzo[b]furan chalcone derivatives **6a-6g** described in this paper were prepared according to the synthetic route **(Scheme- I)**. The structures of the synthesized intermediates and new benzo[b]furan derivatives were confirmed by ^{1}H NMR, mass and IR data. Iodination of 3,5-dimethoxy phenol (**1**) was carried out using iodine in presence of catalytic quantity of cerric ammonium nitrate in acetonitrile at room temperature for 7 h to obtain the iodide compound **2**. Acetylation of iodophenol (**2**) was carried out in presence of acetic anhydride in pyridine to afford the corresponding acetate derivative **3**. Sonogashira coupling of compound **3** with 1-ethynyl-4-methoxybenzene in presence of $Pd(PPh_3)_2Cl_2$/CuI catalyst load followed



Scheme-I: Synthesis of benzo[b]furan derivatives **6a-6g**

TABLE-1
ANTIBACTERIAL ACTIVITY OF INTERMEDIATES AND COMPOUNDS **6a-6g**

Compound No.	Gram-negative bacteria		Gram-positive bacteria	
	E. coli MTCC 443	*P. aeruginosa* MTCC 424	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
2	18	17	21	17
3	–[b]	–	–	–
4	19	17	20	17
5	23	18	24	17
6a	26	23	27	23
6b	26	21	27	21
6c	27	22	26	21
6d	19	17	20	17
6e	18	17	21	17
6f	–	–	–	–
6g	–	–	–	–
Norfloxacin[a]	25	19	25	19

[a]Concentration: 25 µg/mL of DMSO; [b]–No activity

by the intramolecular cyclisation in presence of potassium carbonate resulted in the formation of benzo[b]furan[5]. Treatment of commercially available benzoic acids with $SOCl_2$ followed by the addition of **5** and tin(IV) chloride, using the Friedel Crafts procedure furnished compounds **6a-6g**.

Experimental conditions: (a) I_2, Cerric ammonium nitrate, acetonitrile, room temperature, 7 h; (b) Ac_2O, pyridine, r.t., 2 h; (c) 1-ethynyl-4-methoxybenzene, $Pd(PPh_3)_2Cl_2$, CuI, triethylamine, DMF, 100 °C, 5 h; (d) K_2CO_3, Methanol, 60 °C, 16 h; (e) PhCOCl (a-g), $SnCl_4$, dichloromethane, room temperature, 3 h.

Anti-bacterial activity: The antibacterial activity result (Table-1) revealed that benzo[b]furan derivatives **6a-6g** and its intermediates **1-5**, showed varying pattern of inhibition against the tested microorganisms. In general, it is observed that benzo[b]furan derivatives **6a**, **6b**, **6c** having R = 2,4-dimethoxy phenyl, 2,4,6-trimethoxy phenyl and 3,4,5-trimethoxy phenyl rings, respectively displayed excellent activity against, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*, while compound **5** (having benzo[b]furan motif) showed good activity and the compound **2** (having -OH group) and compound **4** (having acetate group), compounds **6d**, **6e** having 2-methoxy and 4-methoxy moieties exhibited moderate activity. The remaining compounds **3**, **6f** and **6g** were found to be inactive when tested against all the bacterial strains.

Conclusion

The present paper describes the synthesis, spectroscopic identification and antibacterial activity of benzo[b]furan derivatives (**6a-6g**) prepared from commercially available 3,5-dimethoxyphenol and 1-ethynyl-4-methoxybenzene (**Scheme-I**) and tested for antibacterial activity., it is observed that benzo[b]furan derivatives **6a**, **6b**, **6c** having R = 2,4-dimethoxy phenyl, 2,4,6-trimethoxy phenyl and 3,4,5-trimethoxy phenyl rings, respectively displayed excellent activity against, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*, while compound **5** (having benzo[b]furan motif) showed good activity and the compound **2** (having -OH group) and compound **4** (having acetate group) exhibited moderate activity.

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