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Research Paper

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF C(14)-SULFONYL ESTER-TYPE ANDROGRAPHOLIDE DERIVATIVES

Deepthi Agarwal and Poonam Singh

V.N.S Institute of Pharmacy,
VNS Campus Vidya Vihar, Neelbud, Bhopal,
MadhyaPradesh, India, 462045.

Abstract

The labdane diterpenoid Andrographolide is a major secondary metabolite of the plant *Andrographis paniculata*. Andrographolide and its derivatives have attracted the attention of synthetic chemists for their antibacterial, antifungal, anticancer and central nervous system activities. As a part of our present research, a new series of sulfonyl-type of andrographolide derivatives were synthesized from andrographolide. The derived analogs (4a-4g) were evaluated for their antimicrobial activity against *E. coli*, *K. pneumonae* (*Gram Negative bacteria*) and *S. aureus*, *B. subtilis* (*Gram Positive*) bacterial strains, with Ampicillin as standard drug. Most of the analogues show significant antibacterial activity against tested bacterial strains. The methyl sulfonyl derivative 4a had higher inhibitory than parent compound andrographolide 1, and standard drug Ampicillin.

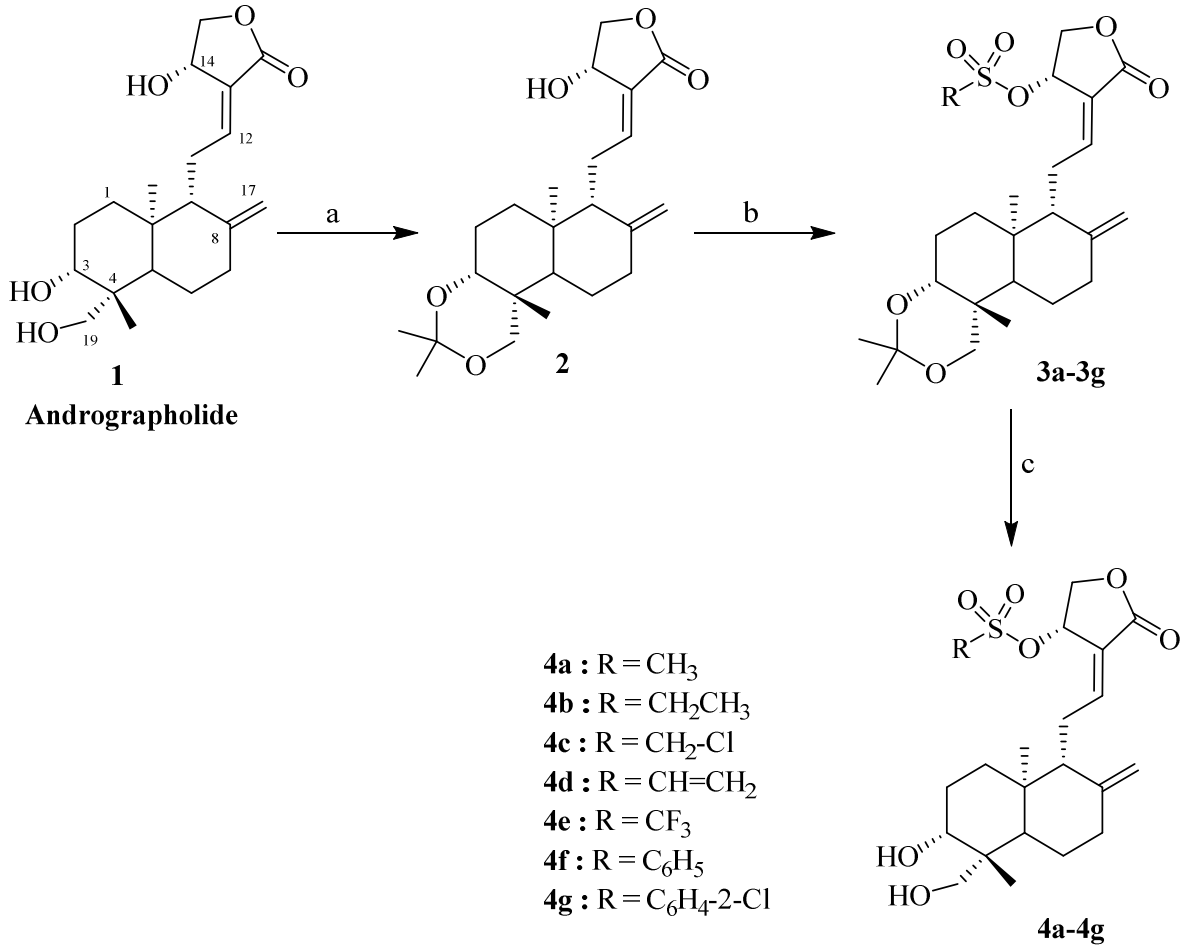
Key words: Andrographolide, *Andrographis paniculata,* antibacterial activity, sulfonyl ester derivatives.

INTRODUCTION

The major metabolite labdane diterpenoid andrographolide (**1**) was isolated from the leaves of *Andrographis paniculata* (family Acanthaceae). It is broadly used in the traditional system of medicine in south east Asia since antiquity [1]. Extracts of plants and their major metabolites including andrographolide (**1)** have been reported to exhibit a wide range of biological activities [2-44] of therapeutic importance that include anti-inflammatory, hepatoprotective, antimalarial, antibacterial, antithrombotic, immune stimulant, antidepressive, antiallergic, central nervous system disorders [15, 17, 19, 21, 26-31], anti HIV, and anticancer. Since its discovery, plethora of biological activities has been evaluated for andrographolide and its derivatives. A huge number of andrographolide (**1**) analogs have been prepared by semi-synthesis for the modification of the biological activities which are available in the literature [9-44]. Presuming that incorporation of sulfonyl esters at C(14) in andrographolide might generate some bioactive molecules, herein, we report the synthesis of a new series of sulfonyl ester andrographolide derivatives and their antibacterial activity against *E. coli*, *K. pneumonae* (*Gram Negative bacteria*) and *S. aureus*, *B. subtilis* (*Gram Positive*) bacterial strains, with Ampicillin as control drug.

MATERIALS AND METHODS

Andrographolide (**1**) was isolated in high yields from the plant of *Andrographis paniculata* and used as the starting material for the preparation of the C(14)-modified sulfonyl analogue library **4a-4g** (Scheme 1). Initially, Andrographolide **1** was treated with 2, 2-dimethoxy propane in the presence of pyridinium *p*-toulenesulfonate (PPTS), Carbon tetrabromide [35] in CH_2Cl_2 at 40°C to yield 87% of compound **2**. Compound **2** was treated with appropriate sulfonyl halides in the presence of diisopropylethyl amine base in DCM to give compounds **3a-3g**. Derivatives **4a-4g** were prepared in yields of 69-75% by reacting compounds **3a-3g** with acetic acid in water to remove isopropylidene (Scheme 1).



Scheme 1. Synthesis of sulfonylester-type andrographolide analogs **4a-4i**. Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, DCM, CBr_4, reflux at 40°C, 1h; (b) appropriate sulfonyl chloride, Et_3N, dry DCM, N_2, r.t, 3-4 h; (c) Acetic acid, H_2O, r.t, 30 min.

RESULTS AND DISCUSSION

Andrographolide (**1**) and its sulfonyl ester type analogs (**4a-4g)** were evaluated for their *in vitro* antimicrobial activity against *E.coli*, *K.pneumonae* (*Gram Negative bacteria*) and *S.aureus*, *B.subtilis* (*Gram Positive*) bacterial strains. The Minimum Inhibitory Concentration (MIC) of the derived compounds (**4a-4g**) against all bacterial strains is determined by liquid dilution method [45]. The antimicrobial activity data of **1** and its analogs are collated in Table 1. For comparison purpose, MIC values of positive control, Ampicillin against bacterial strains are included in the Table 1. Most of the synthesized sulfonyl ester derivatives showed appreciable antimicrobial activity compared to the parent compound Andrographolide **1** against tested bacterial strains. Analogs **4a** and **4b** have also shown significant inhibitory activity (MIC range 2.5 µg/mL - 5 µg/mL) than the standard Ampicillin and parent compound Andrographolide **1**.

Table 1. Minimum Inhibitory Concentration (MIC) in µg/mL of Antimicrobial activity for andrographolide analogues (**4a-4g**) against bacterial strains

MIC (µg/mL)				
	Gram negative		*Gram positive*	
Compound	*E. coli*	*K.pneumonae*	*S. aureus*	*B. subtilis*
1	10	15	15	5
4a	2.5	5	5	2.5
4b	5	5	2.5	5
4c	30	25	25	35
4d	20	15	30	20
4e	15	25	30	20
4f	30	30	35	30
4g	25	15	20	5
Ampicillin	5	5	10	5

Antimicrobial activity and Minimum inhibitory concentration (MIC) determination: The newly synthesized andrographolide derivatives are evaluated for their in vitro antimicrobial activity against *E.coli*, *K.pneumonae* (Gram Negative bacteria) and *S.aureus*, *B.subtilis* (Gram Negative) bacterial strains with Ampicillin as a standard drug. The MIC of the derived compounds (**4a-4g**) against all bacterial strains is determined by liquid dilution method [18-20]. Stock solutions of tested compounds with 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/mL concentrations are prepared with appropriate solvent. The solutions of control drugs, Ampicillin is prepared in the same concentrations. Inoculums of the bacterial culture are also prepared. The MIC at which no growth is observed is taken as the MIC values and the details are presented in table 1. Among the series of newly synthesized andrographolide derivatives 4a and 4b exhibited significant inhibitory activity (MIC range 2.5 µg/ mL- 5 µg/ mL) against all the bacterial strains even than parent compound and control drug Ampicillin (5 -10 µg mL-1), while compounds **4c-4g** also exhibited appreciable inhibitory activity (MIC range 5 µg/ mL) to moderate (MIC range 35 µg/ mL) inhibitory activity.

In summary, a series of new sulfonyl ester-type analogs of andrographolide were synthesized in an effort to explore the antimicrobial effects of C-14 substitution against *E.coli*, *K. pneumonae* (Gram Negative bacteria) and *S. aureus*, *B. subtilis* (Gram Negative) bacterial strains. Most of the analogs showed significant antimicrobial activity against tested bacterial strains compared to the parent andrographolide. Analogs methyl sulfonyl derivative **4a** and ethyl sulfonyl derivative **4b** have higher antimicrobial activity than parent compound andrographolide against all bacterial strains.

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^{1}H-NMR, ^{13}C-NMR and MS data for synthesized compounds:

Methylsulfonyl-andrographolide derivative **(4a)**. White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (t, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 5.8 Hz, 1H), 4.92 (s, 1H), 4.56-4.52 (m, 2H), 4.25-4.16 (m, 2H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.70 (s, 3H), 3.52-3.49 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 3.18 (s, 2H), 2.51-2.31 (m, 4H), 1.99-1.94 (m, 1H), 1.80-1.71 (m, 5H), 1.32-1.15 (m, 6H), 0.69 (s,

3H). ^{13}C NMR (100 MHz, CDC_{l3}): δ 174.9, 168.6, 165.1, 152.2, 148.6, 124.2, 109.1, 80.9, 72.6, 70.3, 63.9, 62.1, 57.2, 55.9, 52.6, 43.9, 39.9, 38.2, 37.2, 29.4, 26.3, 25.7, 23.4, 16.1. HRESIMS *(m/z)*: $[M+H]^+$ calculated for $C_{21}H_{32}O_7S$, 429.1941; found, 429.1936.

Ethylsulfonyl-andrographolide derivative (**4b**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (t, *J* = 6.8 Hz, 1H), 5.99 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.11 (m, 4H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 3.19 (s, 2H), 2.51-2.31 (m, 4H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 169.7, 165.3, 152.9, 148.7, 124.5, 109.2, 80.8, 72.8, 70.4, 63.7, 61.3, 58.2, 55.7, 52.3, 43.8, 39.8, 38.1, 37.3, 29.5, 26.4, 25.3, 23.8, 14.6, 16.4. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{34}O_7S$, 443.2154; found, 443.2143.

Chloromethylsulfonyl-andrographolide derivative (**4c**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (t, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.11 (m, 4H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 3.21 (s, 3H), 2.51-2.31 (m, 4H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.36 (s, 9H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 169.3, 164.9, 152.2, 148.1, 124.4, 109.1, 82.3, 80.8, 72.9, 70.6, 63.6, 58.1, 55.6, 52.3, 43.8, 39.9, 38.2, 37.4, 28.9 (3×*t*-$\underline{C}H_3$), 29.4, 26.4, 25.3, 23.6, 16.8. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{31}ClO_7S$, 464.1419; found, 464.1403.

Vinylsulfonyl- andrographolide derivative (**4d**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (t, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.11 (m, 4H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 2.84-2.69 (m, 4H), 2.51-2.31 (m, 4H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.36 (s, 9H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 169.1, 165.3, 151.9, 148.9, 123.3, 108.9, 80.7, 72.5, 70.2, 63.8, 62.2, 57.3, 55.8, 51.8, 43.8, 39.8, 38.2, 37.1, 29.5, 29.2, 26.4, 25.4, 23.6, 16.3. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{32}O_7S$, 441.1913; found, 441.1904.

Trifloromethylsulfonyl-andrographolide derivative (**4e**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (t, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.09 (m, 6H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 2.83-2.68 (m, 4H), 2.51-2.31 (m, 4H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.29 (t, 3H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 169.1, 165.3, 151.9, 148.9, 123.3, 108.9, 80.7, 72.5, 70.2, 63.8, 61.7, 62.2, 57.3, 55.8, 43.8, 39.8, 38.2, 37.1, 29.6, 29.4, 26.4, 25.4, 23.6, 16.3, 14.1. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{29}F_3O_7S$, 483.1612; found, 483.1608.

Phenylsulfonyl-andrographolide derivative (**4f**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.42 (m, 5H), 7.03 (t, *J* = 6.8 Hz, 1H), 5.96 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.09 (m, 6H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.63 (s, 3H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 2.83-2.68 (m, 4H), 2.55-2.29 (m, 10H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.29 (t, 3H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 171.1, 168.3, 151.9, 148.9, 134.5, 128.3, 123.3, 108.9, 80.7, 72.5, 70.2, 63.8, 62.2, 57.3, 55.8, 51.9, 43.8, 39.8, 38.2, 37.1, 29.5, 29.2, 26.4, 25.4, 33.9, 33.4, 20.1, 16.3. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{34}O_7S$, 491.2132; found, 491.2127.

Ortho-phenylsulfonyl-andrographolide derivative (**4g**). White amorphous powder, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.46 (m, 4H), 7.02 (t, *J* = 6.8 Hz, 1H), 5.97 (d, *J* = 5.8 Hz, 1H), 4.90 (s, 1H), 4.57-4.52 (m, 2H), 4.26-4.09 (m, 6H), 3.92 (d, *J* = 11.6 Hz, 1H), 3.64 (s, 3H), 3.51-3.46 (m, 1H), 3.32 (d, *J* = 10.6 Hz, 1H), 2.83-2.68 (m, 4H), 2.55-2.29 (m, 10H), 1.99-1.94 (m, 1H), 1.79-1.71 (m, 5H), 1.65-1.61 (m, 4H), 1.29 (t, 3H), 1.34-1.12 (m, 9H), 0.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 171.1, 168.3, 151.9, 148.9, 128.1, 126.1, 123.3, 108.9, 80.7, 72.5, 70.2, 61.9, 62.2, 57.3, 55.8, 43.8, 39.8, 38.2, 37.1, 29.5, 29.2, 26.4, 25.4, 34.4, 34.1, 24.3, 24.1, 16.3. HRESIMS (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{33}ClO_7S$, 526.1645; found, 526.1639.

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