



Synthesis of (6-hydroxy-4-phenyl-1, 4-dihydronaphthalen-1-yl) Amino Derivatives by Chalcone Routes

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ABSTRACT

Lignans are naturally occurring compounds which exhibit anticancer, anti-AIDS, and other biological activities. In the present work, new tetralin intermediates of 6-hydroxy-4-phenyl-1, (4-dihydronaphthalen-1-yl) amino derivatives were synthesized in very good yields by the chalcone route. All the products were characterized by spectral and elemental analysis data. The synthesized compounds were analyzed for antiviral activity.

Key words: Podophyllotoxin, Aryl tetraline, Aldol condensation, Simmon smith reaction.

1. INTRODUCTION

The Lignans are a large family of secondary metabolites widely encountered in the plant kingdom. Within this large family of lignans are the aryltetralin lignans 1 and 2 and aryltetralin lignan lactones 3-5 (Figure 1), which have long been recognized as particularly important natural products [1-5].

The most prominent member of this group of natural products is podophyllotoxin (5). This compound, together with analogues 6-8 are aryltetralin lignan lactones isolated from the American Mayapple (*Podophyllum peltatum*) and related Indian species (*Podophyllum emodi*) (Figure 2).

These aryltetralin based compounds exhibit biological screening such as antimalarial, antifungal, antibacterial, antimutagenic, anti-inflammatory, anticancer, and anti-HIV (AIDS). Researchers had been many synthetic modifications to the podophyllotoxin structure including the generation of the three potent anticancer agents 9, 10, and 11 (Figure 3). Etoposide (9) and teniposide (10) are DNA topoisomerase II inhibitors presently in clinical use for the treatment of many cancers [2,6-15]. In the present study, we have synthesized aryltetralin analogues by the chalcone route.

2. CHEMISTRY

In the present work, the chalcone route has been chosen with the slight modified experimental procedure to synthesize tetralone ester intermediates and podophyllotoxin analogues and (Scheme 1), the

starting material (12a-c) brought by Sigma-Aldrich commercially. Chalcones 13a-c were prepared in excellent yields by Claisen condensation reaction of acetophenone (12a-c) with 3, 4, 5-trimethoxy benzaldehyde in the presence of sodium hydroxide in a water-ethanol mixture. Cyclopropyl keto esters (14a-c) were prepared in good yields by the reaction of chalcones 13a-c with dichlorobenzene in Zn-Cu couple using ether as a solvent. The structure of the compound was based on infrared (IR), ¹H nuclear magnetic resonance (NMR), mass spectra, and elemental analysis data. Tetralone ester intermediates were prepared in good yields by the intramolecular Friedel-Crafts alkylation reaction of cyclopropyl keto esters 14a-c in the presence of anhydrous stannic chloride and acetic anhydride in dry dichloromethane. The structure of tetralone esters were based on IR, ¹H NMR, mass spectra, and elemental analysis data [4].

3. EXPERIMENTAL SECTION

Melting points were determined by the open capillary method and are corrected. The IR spectra were recorded on a Fourier transform-IR in KBr disc. The ¹H NMR spectra were recorded on Joel 60 MHz and Joel GSX-400 spectrophotometer using dimethyl sulfoxide as solvent and tetramethylsilane as an internal reference. The chemical shifts are expressed in δ values.

The purity of the compounds is checked by thin layer chromatography on silica gel glass plates in benzene and ethyl acetate as a solvent mixture (7:0.5). The compounds were purified by column chromatography

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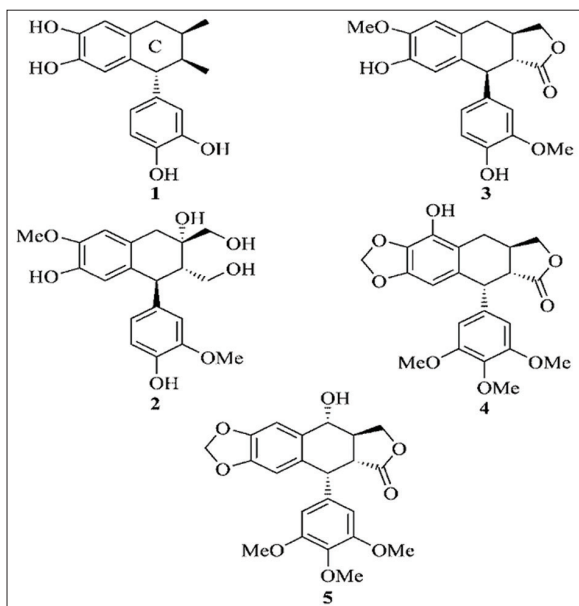


Figure 1: Typical examples of aryltetralin lignans.

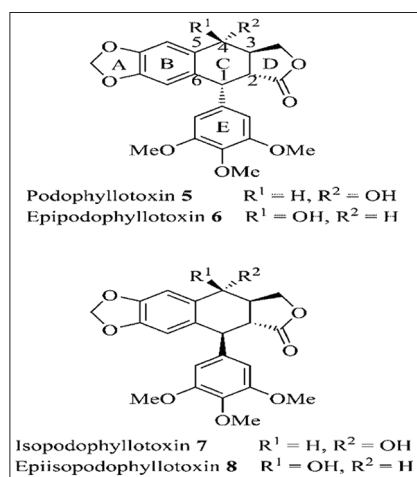


Figure 2: Podophyllotoxin and transfused stereoisomers.

using silica gel (60-120 mesh) as adsorbent and benzene as eluent and by repeated recrystallized from ethanol or methanol [4]. The synthesized compounds were screened for antifungal activity. The results are summarized in Table 1.

3.1. Antifungal Activity

The *in vitro* antifungal activity was carried out against seven fungi by Agar well diffusion method [13]. Compounds (7, 8, and 9) have been tested for their antifungal activity against *Trichoderma harzianum*, *Aspergillus niger*, *Colletotrichum capsici*, *Aspergillus tamari*, *Aspergillus flavus*, *Alternaria solani*, and *Penicillium oxalicum*, at five concentrations of 20, 40, 60, 80, and 100 $\mu\text{g/ml}$ in chloroform. Potato dextrose agar plates were seeded with the test fungi into the surface of the medium uniformly spread using sterile cotton bud. About 50 μl (500 $\mu\text{g/well}$) of each

compound was loaded into the well (6 mm diameter) made by sterile cork borer, then the plates were covered with par film incubated at 27°C for 7 days. Nystatin and sterile distilled water were used as positive and negative control all over the experiment of 50 μg concentration.

4. GENERAL PROCEDURE FOR THE SYNTHESIS

Commercially available acetophenone 12a-c (6.2 mmol) on claisen condensation with 3,4,5-trimethoxy benzaldehyde (6.2 mmol) give the yellow crystalline chalcone 13a-c (5 g, 0.0196 mole), which on reaction with dichlorobenzene in Zn-Cu (0.005 mole) couple using ether as solvent (20 ml) followed by usual work up yield a dark brown color semi-solid 14a-c. The obtained compound which on reaction with Lewis acid, i.e., stannic chloride (3.826 g, 0.0146 mole) using acetic anhydride (2.98 g, 0.0292 mole) in nitrobenzene (50 ml) followed by work up yield compound 15a-c which on reduction with NaBH_4 followed by brominating yield dark gray color product. The obtained product was reacted with amino acids which gives the product of 16a-c and 17a-c [2].

8-phenyl-5-(phenylamino)-5, 6, 7, 8-tetrahydr onaphthalen-2-ol 16a: Pale yellow precipitate in 80% yield, m.p. = 80-86°C, IR (KBr): 3200 cm^{-1} (NH stretching), 2900 cm^{-1} (aliphatic C-H), 1393-1395 cm^{-1} (O-H bends), 1600 (C=C).

^1H NMR (CDCl_3): 3.0-3.4 (m, 2H, $\text{C}_2, \text{C}_3\text{-H}$), 3.7-3.8 (s, 18H, OCH_3), 4.1 (d, 1H, NH), 4.3 (d, 1H, $\text{C}_1\text{-H}$ J=6Hz), 4.8-5.0 (d, 1H, J=4Hz $\text{C}_4\text{-H}$), 6.6-6.7 (m, 2H $\text{C}_2^1, \text{C}_6^1\text{-H}$), 6.5-6.6 (m, 2H $\text{C}_2^{11}, \text{C}_6^{11}\text{-H}$), 7.0-7.20 (m, 3H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.50-7.65 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 3.8 (q, 3H), 2.2 (d, 3H)

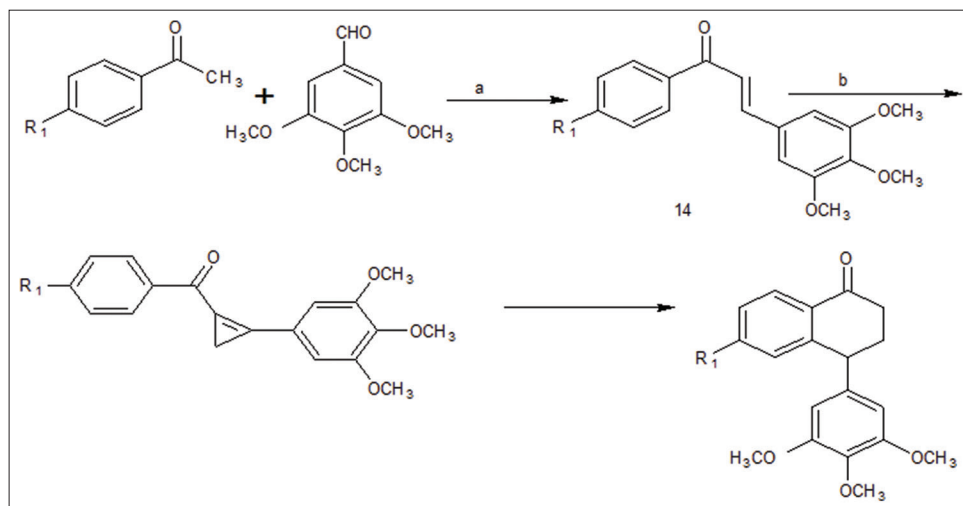
Mass spectra (m/e, % abundance): 493 (m^+), 494 ($\text{m}^+ + 1$)

Molecular mass $\text{C}_{22}\text{H}_{21}\text{NO}$; C, 80.92; H, 6.40%; Found C, 80.86; H, 6.42%

6-nitro-*N*,4-diphenyl-1,2,3,4-tetrahydronaphthalen-1-amine

16b: Yellow crystalline compound in 78% yield, m.p. = 80-82°C, IR (KBr): 3400 cm^{-1} (NH stretching), 2900 cm^{-1} (aliphatic C-H), 1395 cm^{-1} (O-H bends), 1600 (C=C), 1605 (CO) cm^{-1} .

^1H NMR (CDCl_3): δ 3.0-3.1 (m, 2H, $\text{C}_2, \text{C}_3\text{-H}$), 3.7-3.8 (s, 18H, OCH_3), 3.4-3.5 (s, 6H, $\text{C}_2, \text{C}_3\text{-OCH}_3$) 4.1 (d, 1H, NH), 4.3 (d, 1H, $\text{C}_1\text{-H}$ J=6Hz), 4.8-5.0 (d, 1H, J=4Hz $\text{C}_4\text{-H}$), 6.6-6.7 (m, 2H $\text{C}_2^1, \text{C}_6^1\text{-H}$), 6.5-6.5 (m, 2H $\text{C}_2^{11}, \text{C}_6^{11}\text{-H}$), 7.0-7.20 (m, 3H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 3.8 (q, 3H), 2.2 (d, 3H).



Scheme 1: (a) NaOH, C₂H₅OH-H₂O, rt, (b) CH₂I₂, Zn-Cu couple, ether, (c) anhydrous SnCl₂, dry C₆H₅NO₂, Ac₂O, (d) NaBH₄, methanol, HBr, CH₃CN, amino acid, BU₄NI, Et₃N, THF.

Mass spectra (m/e, % abundance): 493(m⁺), 494(m⁺+1)

Molecular mass C₂₃H₂₉N₀ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

6-chloro-*N*,4-diphenyl-1,2,3,4-tetrahydronaphthalen-1-amine

16c: orange color precipitate compound in 68% yield, m.p=130-132°C.

IR (KBr): 3330 cm⁻¹ (NH stretching), 2800 cm⁻¹ (aliphatic C-H), 1440 cm⁻¹ (O-H bends), 1600 (C=C), 1657 (CO) cm⁻¹

¹H NMR(CDC₁₃): d 2.8-3.0 (m, 2H, C₂, C₃-H), 3.7-3.8 (s, 18H, OCH₃), 4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.6 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 3H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.50-7.65 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 3.8 (q, 3H), 2.2 (d, 3H)

Mass spectra (m/e, % abundance): 461 (m⁺), 462 (m⁺+1)

Molecular mass C₂₂H₂₀NCl; C, 80.92, N; 6.40%: Found C, 80.86; H, 6.42%.

5-[(3-methylphenyl)amino]-8-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

17a: 60% yield, m.p.= 76-80°C,

IR (KBr): 3450 cm⁻¹ (NH stretching),

2900 cm⁻¹ (aliphatic C-H),

1397 cm⁻¹ (O-H bends), 1600 (C=C), 1637 (CO) cm⁻¹

¹H NMR (CDC₁₃): δ 2.90-3.44 (m, 2H, C₂, C₃-H), 2.35-2.37 (s, 18H, OCH₃), 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6 Hz), 4.8-5.0 (d, 1H, J=4 Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 6H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 4.2 (t, 2H)

Mass spectra (m/e, % abundance): 493 (m⁺), 494 (m⁺+1)

Molecular mass C₂₃H₂₃NO; C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

N-(3-methylphenyl)-6-nitro-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine

17b: 70% yield, m.p. = 96-98°C.

IR (KBr): 3657 cm⁻¹ (NH stretching), 2800 cm⁻¹ (aliphatic C-H), 1440-1395 cm⁻¹ (O-H bends), 1620 (C=C).

¹H NMR (CDC₁₃): δ 3.2-3.59 (m, 2H, C₂, C₃-H), 3.7-3.8 (s, 18H, OCH₃), 3.2-3.5 (s, 6H, C₂, C₃-OCH₃), 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 6H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 4.2 (t, 2H)

Mass spectra (m/e, % abundance): 493 (m⁺), 494 (m⁺+1)

Molecular mass C₂₃H₂₂N₂O₂ C, 80.92; H, 6.40%: Found C, 80.86; H, 6.42%.

6-chloro-*N*-(3-methylphenyl)-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine

17c: 60% yield, m.p.= 96°C.

Table 1: Compound 17a dissolved in chloroform in different concentration.

Conc. in ug/ml	Fungi (zone of inhibition in mm)																				
	A			B			C			D			E			F			G		
	N	S	Ct	N	S	Ct	N	S	Ct	N	S	Ct	N	S	Ct	N	S	Ct	N	S	Ct
20	14	12	10	10	22	14	13	17	16	10	15	14	10	17	13	11	16	14	27	26	17
40	14	11	10	22	14	13	17	17	10	15	13	10	17	15	11	16	14	09	27	27	17
60	14	13	10	22	13	13	17	14	10	15	12	10	17	15	11	16	12	09	27	25	17
80	14	13	10	22	15	13	17	14	10	15	12	10	17	12	11	11	16	13	27	23	17

A=Trichoderma harzianum, B=Aspergillus niger, C=Collectotrichum capsici, D=Aspergillus tamarii, E=Aspergillus flavus, F=Alternaria solani, G=Penicillium oxalicum, N=Nistatin, positive control, S=Zone of inhibition of compound, Ct=Distilled water, negative control

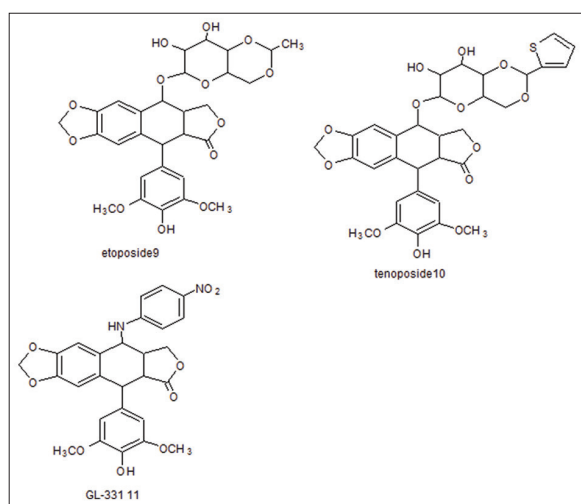


Figure 3: (a) NaOH, C₂H₅OH-H₂O, rt (b) CH₂I₂, Zn-Cu couple, ether (c) Anhydrous SnCl₂, dry C₆H₅NO₂, Ac₂O (d) NaBH₄, methanol, HBr, CH₃CN, amino acid, BU₄NI, Et₃N, THF.

IR (KBr): 3140 cm⁻¹ (NH stretching), 2900 cm⁻¹ (aliphatic C-H), 1440-1395 cm⁻¹ (O-H bends), 1600 (C=C), 1617 (CO) cm⁻¹

¹H NMR (CDCl₃): δ 2.9-3.0 (m, 2H, C₂, C₃-H), 3.7-3.8 (s, 18H, OCH₃), 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 6H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 4.2 (t, 2H)

Mass spectra (m/e, % abundance): 493 (m⁺), 494 (m⁺+1)

Molecular mass C₂₃H₂₂ClN; C, 80.92; H, 6.40%; Found C, 80.86; H, 6.42%.

5-[(3-hydroxyphenyl) amino]-8-phenyl-5,6,7,8-tetrahydronaphthalen-2-ol

18a: 46% (1.22 g) yield, m.p.= 70-73°C.

IR (KBr): 3350 cm⁻¹ (NH stretching), 2800 cm⁻¹ (aliphatic C-H), 1340-1495 cm⁻¹ (O-H bends), 1650 (C=C).

¹H NMR (CDCl₃): δ 3.2-3.4 (m, 2H, C₂, C₃-H), 3.7-3.8 (s, 18H, OCH₃), 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 6H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (d, 2H, k-H), 4.8 (d, 1H, R-COOH), 4.2 (t, 2H)

Mass spectra (m/e, % abundance): 493 (m⁺), 494 (m⁺+1)

Molecular mass C₂₂H₂₁NO₂; C, 80.92; H, 6.40%; Found C, 80.86; H, 6.42%.

3-[(6-nitro-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)amino]phenol 18b: 45% (1.02 g) yield, m.p. = 96-98°C.

IR (KBr): 3450 cm⁻¹ (NH stretching), 2900 cm⁻¹ (aliphatic C-H), 1470-1395 cm⁻¹ (O-H bends), 1680 (C=C).

¹H NMR (CDCl₃): δ 2.8-2.9 (m, 2H, C₂, C₃-H), 3.5 (bs, 18H, OCH₃), 3.2-3.4 (s, 6H, C₂, C₃-OCH₃) 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, 6H, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (bd, 2H, k-H), 4.8 (d, 1H, R-COOH), 3.9 (q, 1H), 2.9 (d, 2H)

Mass spectra (m/e, % abundance): 453 (m⁺), 454 (m⁺+1)

Molecular mass C₂₂H₂₀N₂O₃; C, 80.92; H, 6.40%; Found C, 80.86; H, 6.42%.

3-[(6-chloro-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)amino]phenol 18c: 40% (1.22 g) yield, m.p.= 76°C.

IR (KBr): 3300 cm⁻¹ (NH stretching), 2900 cm⁻¹ (aliphatic C-H), 1450-1395 cm⁻¹ (O-H bends), 1600

(C=C).

¹H NMR (CDCl₃): δ 3.5-3.9 (m, 2H, C₂, C₃-H), 3.7-3.8 (bs, 18H, OCH₃), 3.4-4.1 (d, 1H, NH), 4.3 (d, 1H, C₁-H J=6Hz), 4.8-5.0 (d, 1H, J=4Hz C₄-H), 6.6-6.7 (m, 2H C₂¹, C₆¹-H), 6.5-6.5 (m, 2H C₂¹¹, C₆¹¹-H), 7.0-7.20 (m, SH, Ar-H), 7.20-7.30 (d, 1H, Ar-H), 7.20-7.25 (bd, 2H, k-H), 4.8 (d, 1H, R-COOH), 4.2 (t, 2H)

Mass spectra (m/e, % abundance): 493 (m⁺), 494 (m⁺+1)

Molecular mass For C₂₂H₂₀ClNO, 80.92; H, 6.40%:
Found C, 80.86; H, 6.42%.

5. RESULTS AND DISCUSSION

In this context, we have chosen chalcone route with some changes in the experimental procedure and reagents to synthesize tetralin intermediates. The starting material was obtained by commercially. Chalcone 13a-c were prepared in excellent yields by Claisen condensation reaction of acetophenone 12a-c with 3, 4, 5-trimethoxy benzaldehyde in the presence of sodium hydroxide in a water-ethanol mixture. Cyclopropyl ketones 14a-c was prepared in good yields by simmon smith reaction of chalcone. Tetralone ester intermediates 15a-c was prepared in good yields by the intramolecular Freidel-Crafts alkylation reaction of cyclopropyl ketones 14a-c in the presence of anhydrous Stannic chloride and acetic anhydride in dry dichloromethane. The obtained compound was then treated with sodium borohydride in absolute methanol at 0-5°C for 2 h. The resultant product was done brominating with hydrogen bromide in acetonitrile which contain catalytic amount of ether and molecular sieves at 0°C, and finally, the obtained product was then stirred with amino acids in dry tetrahydrofuran which contain triethylamine and tetra butyl ammonium iodide at room temperature for 4 h to get final product 16a-c, 17a-c, 18a-c. The structure of tetralone intermediates was confirmed by IR, ¹H NMR, and mass spectra data. The synthesized compounds were screened for antiviral activity. The results are summarized in Table 1.

6. CONCLUSION

Successfully, we have synthesized new analogues of tetralins. All compounds were characterized by standard spectroscopic techniques; evaluation of the antiviral activity of all new compounds was carried out and proved significant to moderate activity.

7. ACKNOWLEDGMENTS

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8. REFERENCES

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***Bibliographical Sketch**

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