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Adamantane-pyrido[2,3-d]pyrimidine Derivatives; Synthesis, Characterization and Investigation of Antimicrobial Study

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ABSTRACT

Target molecules based on Adamantane-pyrido[2,3-d]pyrimidine derivatives were prepared. Adamantane-pyrido[2,3-d]pyrimidine series using *N*-(hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-oxo-2*H*-Chromen-3-yl)pyrido[2,3-d]Pyrimidine-3(4*H*) carboxamide (6a-j) was synthesized by reaction between 3-(2-chloroacetyl)-5-(2,4-substitutedphenyl)-2-Methyl-7-(2-Oxo-2*H*-Chromen-3-yl) pyrido[2,3-d]pyrimidin-4(3*H*)-one (5a-j) and 3-aminoadamantan-1-ol. These derivatives of Adamantane-pyrido[2,3-d]Pyrimidine were investigated *In vitro* for their biological characteristics against the strains which were isolated clinically and confirmation of their structure was done by FTIR, ^{1}H-NMR, ^{13}C NMR and LCMS. The newly synthesized derivatives gave promising antimicrobial activity.

Keywords: Adamantane, Pyrido[2,3-d]pyrimidine, Pyrimidine, Chromene, N-hydroxy adamantan-1-yl, 3-aminoadamantan-1-ol, antimicrobial, antifungal.

INTRODUCTION

The research on biochemical importance of pyrimidines and pyrimidine derivatives have centered great importance because of the pyrimidines represent the main backbone in alkaloids and nucleic bases as well as their interesting powerful biological activities. Pyrimidine derivatives contain diversified applications as pharmaceuticals and occupy a unique place in heterocyclic and medicinal chemistry also[1-3]. Combination of coumarin derivatives and pyrimidine derivatives has received considerable attention by researchers because of possessing so many biological important application and pharmacological activities[4-7]. Various pyrimidine derivatives show very broad range of biological activities viz. antimicrobial activity[8], anti-inflammatory[9], anticancer[10], antiviral[11], antitubercular[12], antihypertensive[13-14], anticonvulsant[15], H1-antihistamines[16], 4-phosphodiester inhibitors[17-18] and antimalarial[19-20].

MATERIALS AND METHODS

The synthesis was carried out using A R Grade reagents and solvents and were used without further purification. Open capillary method was used to take melting points and are uncorrected. TLC (thin layer chromatography) was used check the

progress of reactions using silica gel plates GF254 (E. Merck). The solvent system comprised of methanol and toluene; the chromatograms visualized using source of UV light (254nm). FTIR spectra were recorded making use of KBr on pallets Perkin Elmer 1600 FTIR. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker 500 MHz, DMSO-d_6 as the solvent and TMS (tetra methyl silane) as internal standard. LCMS was used to carry out LC-MS.

Synthesis of 3-Acetyl-2H-chromen-2-one (1)

0.01 mole Salicylaldehyde and 0.01 mole EAA (Ethyl Acetoacetate) was mixed in 15 mL in ethyl alcohol. 2 mL DEA (diethyl aniline) was added in this mixture with continuous stirring at RT for about 2 h which yielded solid. The solid was filtered, recrystallized using ethyl alcohol as solvent. Yield; 91%, m.p. 113-115°C.

Preparation of various substituted chalcone derivatives (2a-k)

Base catalyzed Claisen-Schmidt condensation reaction was used to synthesize various chalcone derivatives of the appropriate substituted aldehydes and substituted acetophenone by reported literature method[21].

3-Acetyl-2H-chromen-2-one (0.01mole) (1) and substituted benzaldehyde (0.01mole) dissolved in 10 mL ethanol in RBF using a magnetic stirrer. Water bath was used to maintain the temperature of reaction at 20-25°C. 1 g NaOH in 10 mL dist. H_2O was taken and this NaOH solution was drop wise added into to the reaction mixture for 30 min with continuous stirring. On completion of addition, solution was stirred further for 4-5 h and kept at RT for 12 hours. The final solution was dumped into chilled H_2O and neutralized using 0.1-0.2NHCl whereby solid obtained. The product was filtered & then dried in air. The crude was recrystallized by rectified spirit. Further purification was done by used ethyl acetate and *n*-hexane.

Preparation of various derivatives of 2-Amino-4-(2,4-substitutedphenyl)-6-(2-oxo-2H-chromen-3-yl) nicotinonitrile (3a-k)

Chalcone derivatives (2a-k) (0.01mole), malononitrile (0.01mole) and anhydrous ammonium acetate (0.02mole) were taken in RBF and dissolved in 20 mL absolute ethanol solvent. It was heated under reflux condition for 7-8 hours. Completion of reaction was confirmed by TLC. This reaction mixture was then cooled down to the RT. As solution attained RT, solid was formed which was filtered, then was washed with distilled water till free from impurities dried and ethanol was used for recrystallized to obtains compounds (3a-k)[22].

Preparation of various derivatives of 5-(2,4-sub-stitutedphenyl)-2-Methyl-7-(2-oxo-2H- chromen-3-yl) Pyrido[2,3-d] Pyrimidin-4(3H)-one (4a-k)

The mixture of compound (3a-k) (0.01mole) and excess of glacial CH_3COOH (20 mL) was heated maintaining reflux condition for 7-8 hours. Glacial CH_3COOH was self-solvent. On completion of the reaction, solution obtained was cooled down to RT. The resultant solution was added in to chilled H_2O. The solid formed was filtered, then washed with cold dist. H_2O several times, dried & recrystallization from dioxane yielded compounds (4a-k).

Preparation of various derivatives of 3-(2-Chloroa-cetyl)-5-(2,4-substitutedphenyl)-2-Methyl-7-(2-Oxo-2H- Chromen-3-yl) Pyrido[2,3-d]Pyrimidin-4(3H)-one (5a-k)

Sodium acetate was dissolved in 20 mL glacial acetic acid in RBF. Compound (4a-k) (0.01mole) was dissolved in this mixture and was cooled 0-5°C. Chloroacetyl chloride (0.02 mL) was added in this mixture at 0-5°C during 1 hours. After the completion of addition, resultant solution was stirred for 30 minute. The temperature was raised to 80°C for heating up to 1.5 h & then was stirred at R.T. This solution was dumped into chilled H_2O, the solid thus formed was filtered, washed using chilled H_2O several times, dried, recrystallized from acetic acid to give compounds (5a-k).

Preparation of various derivatives N-(Hydroxyada mantan-1-yl)-5-(2,4-substituted phenyl)-2-Methyl-4-oxo-7-(2-Oxo-2H-Chromen-3-yl)Pyrido[2,3-d] Pyrimidine-3(4H) Carboxamide (6a-k)

Compound (5a-k) (0.01mole) was dissolved in 20 mL DMF. Slow heating was started and mixture of 3-Aminoadamantan-1-ol (0.01mole) and K_2CO_3 (0.012mole) was mixed slot wise. On completion of addition, the resultant solution was refluxed for 5-6 hours. TLC was used to check completion of reaction. The resultant solution was allowed to cool to RT, then dumped into ice, the solid formed was filtered, then washed with dist. H_2O several times, dried, finally recrystallized using ethanol to yield compounds (6a-k).

Reaction scheme

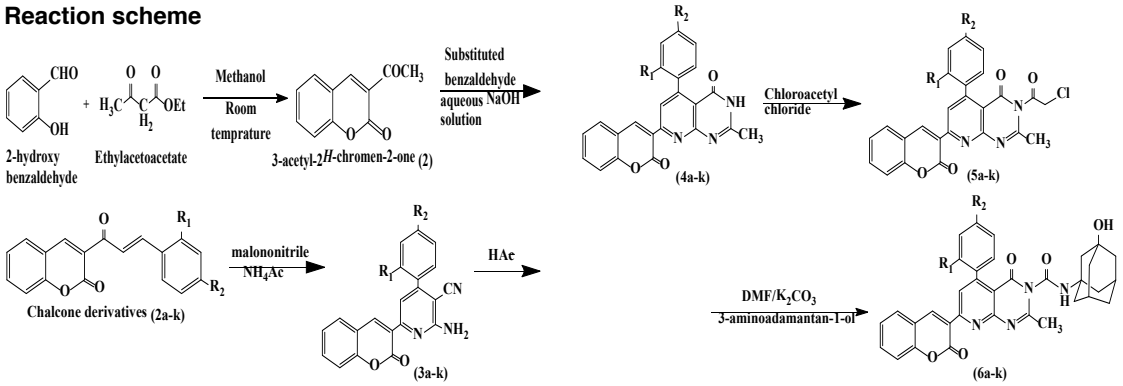


Table 1: Physical properties of synthesized Adamantane-pyrido[2,3-d]pyrimidine derivatives (TT_1 to TT_{11})

No	Sample	Sample Code	Molecular Formula	Substituent		Melting Point(°C)
				R_1	R_2	
1	6a	TT_1	$C_{35}H_{32}N_4O_6$	-H	$-OCH_3$	278-280°C
2	6b	TT_2	$C_{34}H_{29}ClN_4O_5$	-H	-Cl	285-287°C
3	6c	TT_3	$C_{36}H_{35}N_5O_5$	-H	$-N(CH_3)_2$	272-274°C
4	6d	TT_4	$C_{34}H_{30}N_4O_6$	-H	-OH	286-288°C
5	6e	TT_5	$C_{34}H_{29}N_5O_7$	-H	$-NO_2$	275-276°C
6	6f	TT_6	$C_{34}H_{29}BrN_4O_5$	-H	-Br	266-268°C
7	6g	TT_7	$C_{34}H_{30}N_4O_6$	-OH	-H	258-260°C
8	6h	TT_8	$C_{35}H_{32}N_4O_6$	-H	$-CH_3$	288-290°C
9	6i	TT_9	$C_{34}H_{28}Cl_2N_4O_5$	-Cl	-Cl	280-282°C
10	6j	TT_{10}	$C_{35}H_{32}N_4O_6$	$-CH_3$	-H	272-273°C
11	6k	TT_{11}	$C_{34}H_{29}BrN_4O_5$	-Br	-H	255-257°C

Table 2: Elementary analysis data of Adamantane-pyrido[2,3-d]pyrimidine derivatives (TT_1 to TT_{11})

No	Sample Code	Elementary Analysis											
		Calculated (%)						Found (%)					
		C	H	O	N	Cl	Br	C	H	N	O	Cl	Br
1	TT_1	69.52	5.33	15.88	9.27	-	-	69.48	5.27	15.86	9.23	-	-
2	TT_2	67.05	4.80	13.13	9.20	5.82	-	67.00	4.77	13.09	9.18	5.79	-
3	TT_3	70.00	5.71	12.95	11.34	-	-	69.98	5.67	12.89	11.30	-	-
4	TT_4	69.14	5.12	16.25	9.49	-	-	69.10	5.10	16.20	9.42	-	-
5	TT_5	65.91	4.72	18.07	11.30	-	-	65.89	4.69	17.98	11.27	-	-
6	TT_6	62.49	4.47	12.24	8.57	-	12.23	62.47	4.44	12.22	8.55	-	12.19
7	TT_7	69.14	5.12	16.25	9.49	-	-	69.08	5.08	16.14	9.44	-	-
8	TT_8	69.52	5.33	15.88	9.27	-	-	69.49	5.31	15.87	9.25	-	-
9	TT_9	63.46	4.39	12.43	8.71	11.02	-	63.44	4.31	12.35	8.64	10.88	-
10	TT_{10}	69.52	5.33	15.88	9.27	-	-	69.47	5.22	15.81	9.22	-	-
11	TT_{11}	62.49	4.47	12.24	8.57	-	12.23	62.40	4.42	12.21	8.51	-	12.15

Table 3: Antibacterial activity of Adamantane-pyrido[2,3-d]pyrimidine derivatives (TT_1 to TT_{11})

		Antibacterial activity Minimum Inhibition Concentration			
Sample	Sample code	*E. coli* MTCC443	*P. aeruginosa* MTCC1688	*S. aureus* MTCC96	*S. pyogenes* MTCC442
6a	TT_1	50	62.5	100	62.5
6b	TT_2	100	100	200	62.5
6c	TT_3	62.5	50	200	100
6d	TT_4	100	62.5	100	200
6e	TT_5	100	200	200	200
6f	TT_6	50	100	250	200
6g	TT_7	100	200	250	200
6h	TT_8	50	62.5	200	62.5
6i	TT_9	50	100	50	100
6j	TT_{10}	62.5	100	100	100
6k	TT_{11}	100	200	100	200
Ampicillin		100	100	250	100
Chloramphenicol		50	50	50	50
Norfloxacin		10	10	10	10
Ciprofloxacin		25	25	50	50

Table 4: Antifungal activity and antitubercular of synthesized Adamantane-pyrido[2,3-d]pyrimidine derivatives (TT_1 to TT_{11})

		Antifungal activity & Antitubercular activity Minimum Inhibition Concentration			
Sample	Sample code	*C. albicans* MTCC227	*A. niger* MTCC282	*A. clavatus* MTcc1323	H_{37}RVMIC µg/mL
6a	TT_1	100	100	50	100
6b	TT_2	50	62.5	100	62.5
6c	TT_3	200	100	200	100
6d	TT_4	100	100	250	500
6e	TT_5	62.5	50	62.5	100
6f	TT_6	50	100	100	200
6g	TT_7	100	100	200	62.5
6h	TT_8	62.5	100	50	100
6i	TT_9	200	200	200	500
6j	TT_{10}	200	250	100	100
6k	TT_{11}	100	100	100	62.5
Nystatin		100	100	100	-
Griseofulvin		500	100	100	-
Rifampicin		-	-	-	40
Isoniazid		-	-	-	0.2

Table 5: Antimalarial activity of synthesized Adamantane-pyrido[2,3-d]pyrimidine derivatives (TT_1 to TT_{11})

	Antimalarial Activity Minimum Inhibition Concentration	
Sample	Sample Code	Mean Values
6a	TT_1	0.88 µg/mL
6b	TT_2	0.25 µg/mL
6c	TT_3	1.01 µg/mL
6d	TT_4	0.98 µg/mL
6e	TT_5	0.74 µg/mL
6f	TT_6	0.42 µg/mL
6g	TT_7	0.35 µg/mL
6h	TT_8	0.46 µg/mL
6i	TT_9	0.31 µg/mL
6j	TT_{10}	0.52 µg/mL
6k	TT_{11}	0.23 µg/mL
Chloroquine		0.020 µg/mL
Quinine		0.268 µg/mL

^{1}HNMR spectral data of Adamantane-pyrido [2,3-d]pyrimidine derivatives

^{1}H NMR data (500 MHz, DMSO-d_6) δ; 1.57-2.24 (m, 14H of adamantane), 3.47 (s, OH group of admentanol), 7.35 (s, 1H of NH group of adamantane), 3.07 (s, 3H of -CH_3 of pyrimidine), 3.90 (s, 3H of CH_3 of methoxy group), 6.94-8.59 (m, 10H of Aromatic group).

^{1}H NMR data (500 MHz, DMSO-d6) δ; 1.55-2.24 (m, 14H of adamantane), 3.43 (s, OH group of admentanol), 7.41 (s, 1H of NH group of admantan), 3.09 (s, 3H of CH_3 of pyrimidine), 3.92 (s, 6H of $N(CH_3)_2$ group), 6.75-8.51 (m, 10H of Aromatic group).

^{1}H NMR data (500 MHz, DMSO-d_6) δ; 1.55-2.24 (m, 14H of adamantane), 3.55 (s, OH group of admentanol), 7.41 (s, 1H of NH group of admantan), 3.13 (s, 3H of CH_3 of pyrimidine), 7.35-8.60 (m, 10H of Aromatic group).

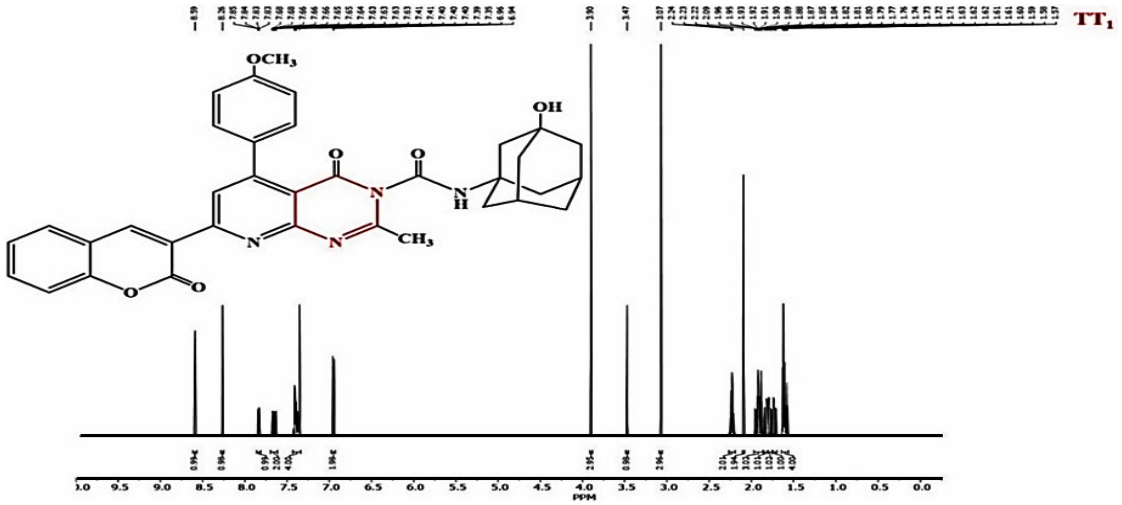


Fig. 1. ^{1}H NMR spectral data of TT_1

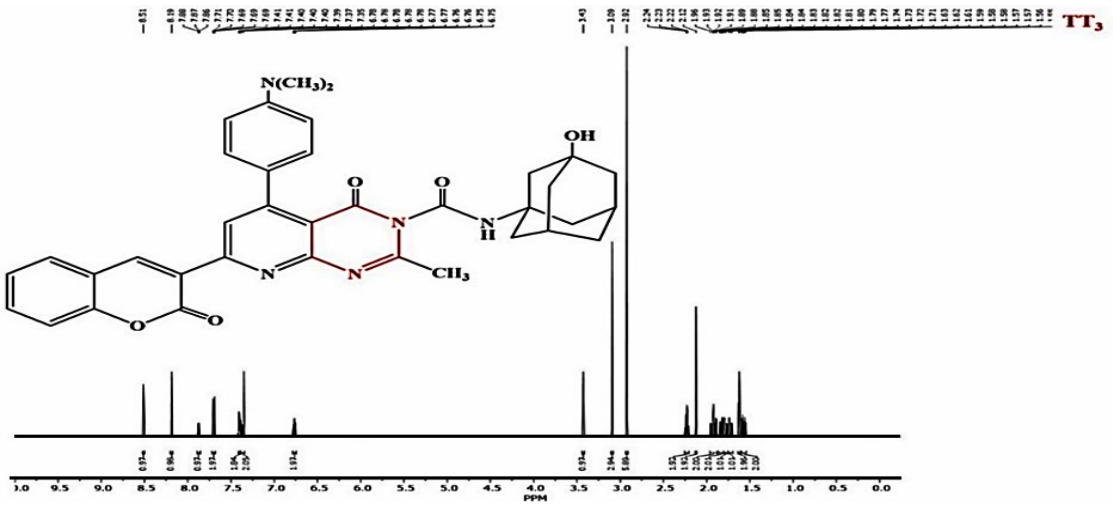


Fig. 2. ^{1}H NMR spectral data of TT_3

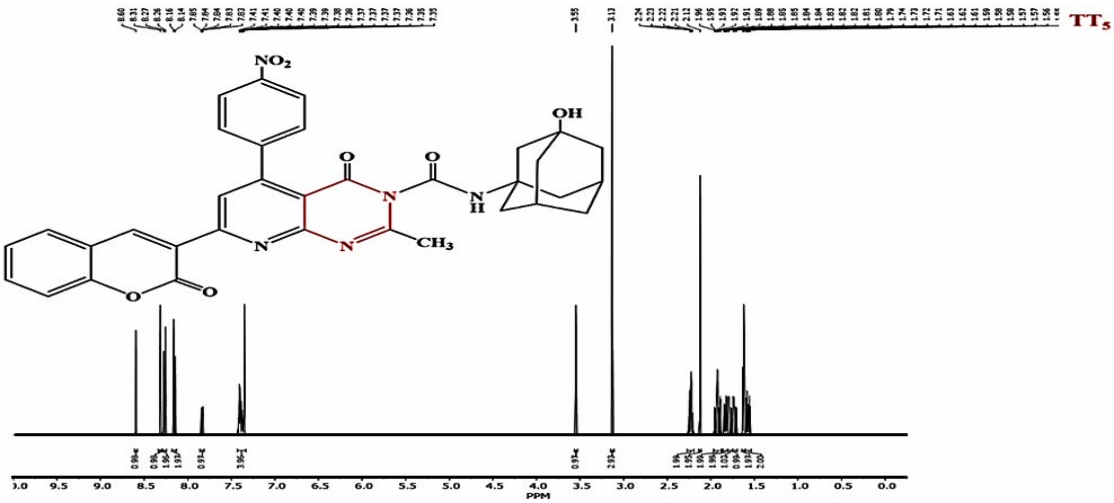


Fig. 3. ^{1}H NMR spectral data of TT5

^{1}H NMR data (500 MHz, DMSO-d_6) δ; 1.55-2.37 (m, 14H of adamantane), 3.55 (s, OH group of admentanol), 7.35 (s, 1H of NH group of admantan), 3.13 (s, 3H of CH_3 of pyrimidine), 7.10-8.60 (m, 10H of Aromatic group), 2.73 (s, 3H of CH_3 group).

^{13}C NMR spectral data of Adamantane-pyrido [2,3-d]pyrimidine derivatives

Compound-TT_2: 22.40, 29.71, 35.98, 43.07, 44.40, 47.56, 50.50, 55.35, 68.80, 113.88, 114.98, 119.95, 120.24, 122.36, 125.51, 127.56, 129.59, 131.33, 132.68, 143.60, 145.30, 148.78, 152.96, 153.90, 154.04, 158.73, 159.49, 163.34, 164.02

IR Spectra of Adamantane-pyrido[2,3-d] pyrimidine derivatives

Compound-TT_1: IR(KBr, cm^{-1}): ν=C-H 1271, N-H 1526 secondary amine, O-H 3924, C-H 2855 of OCH_3, C-H 3413, C-Br 738, C-H 2922 of methyl group.

Compound-TT_3: IR (KBr, cm^{-1}): ν=C-H 1275, N-H 1541 secondary amine, O-H 3926, C-H 3413, C-Br 738, C-H 2925 of methyl group. C-H 2925 of $N(CH_3)_2$

LCMS Spectra of Adamantane-pyrido[2,3-d] pyrimidine derivatives

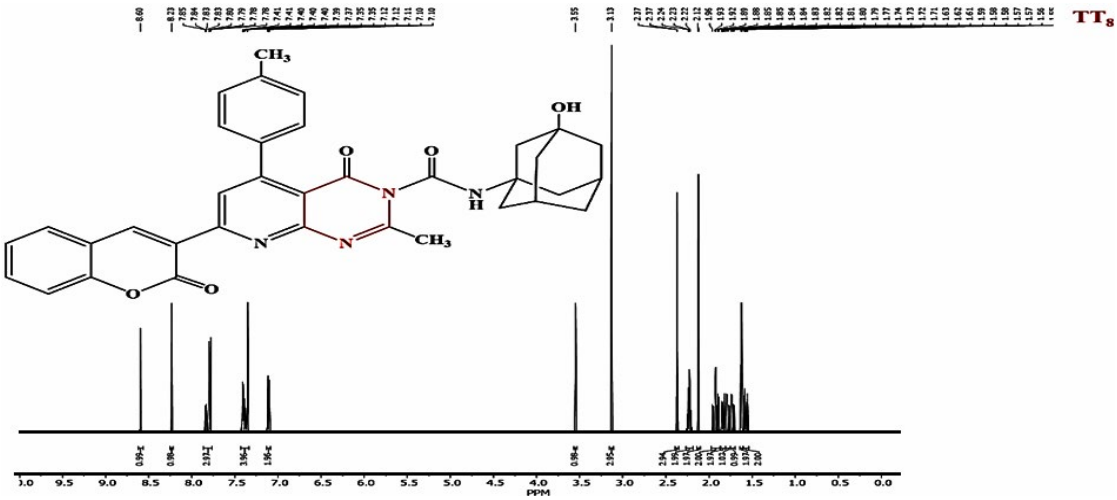


Fig. 4. ^{1}H NMR spectral data of TT_8

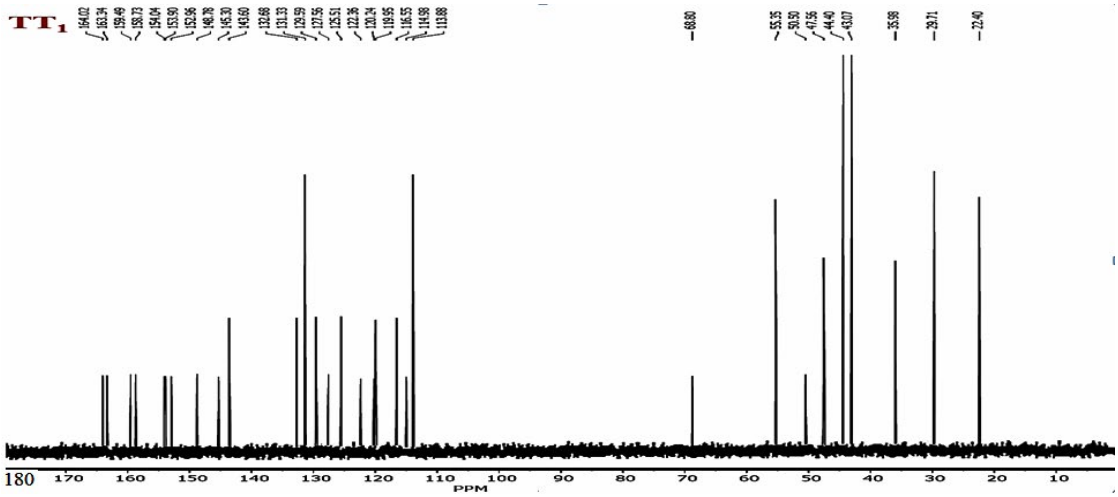


Fig. 5. ^{13}C NMR spectral data of TT_1

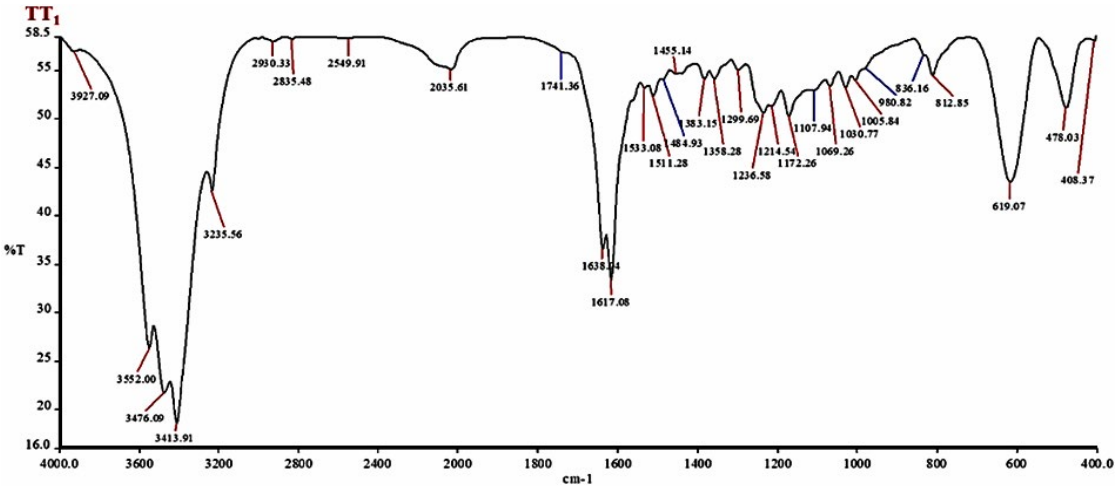


Fig. 6. IR Spectra of TT_1

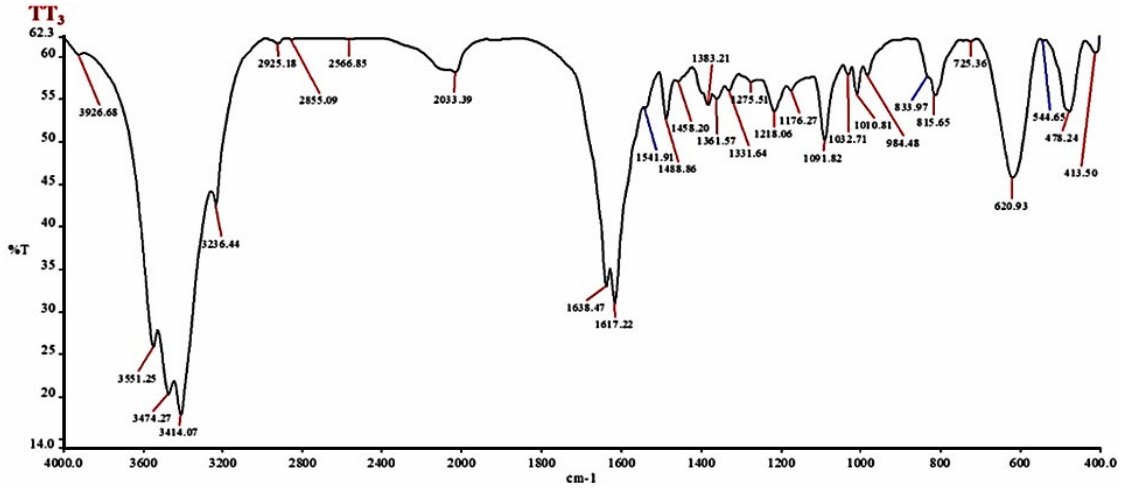


Fig. 7. IR Spectra of TT_3

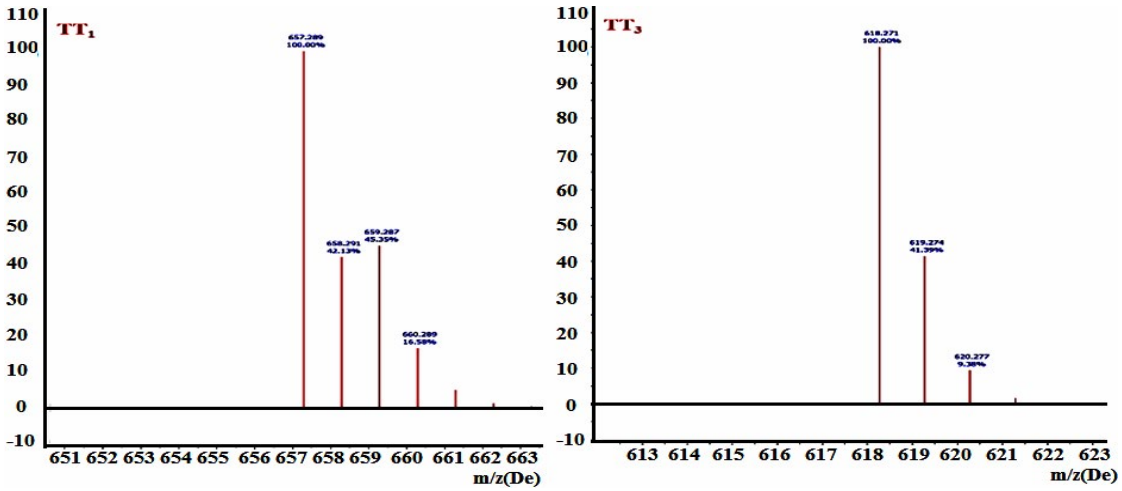
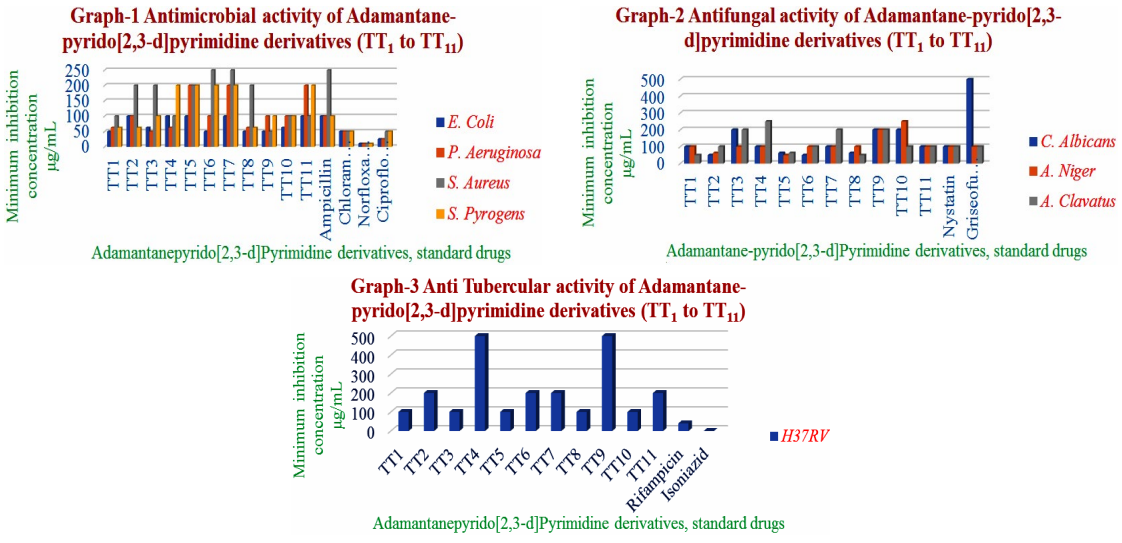


Fig. 8. LCMS Spectra of TT_1 and TT_3



RESULTS AND DISCUSSION

3-Acetyl-2H-Chromen-2-one resulted by the reaction of Ethylacetoacetate (EAA) & Salicylaldehyde. (DEA) Diethyl Aniline then was mixed with continuous stirring dropwise at RT to obtain solid. Various chalcone compounds were prepared using Claisen-Schmidt (base catalyzed) condensation reaction of selected substituted aldehyde and substituted acetophenone by known literature method[19]. Substituted benzaldehyde and 3-Acetyl-2H-Chromen-2-one was mixed in ethanol using magnetic stirrer. Water bath was used to maintain the reaction temperature between 20-25°C on the magnetic stirrer. 1 g NaOH was added to 10 mL distilled water and the resulted aqueous NaOH solution was dropwise added into the to the reaction mixture and when addition was completed this solution was stirred further for 4-5 h and kept for 12 hours. The mixture was made neutral with 0.1-0.2N HCl till the solidification obtained. The resulted mixture was filtered then dried in air finally recrystallized using rectified spirit. Further carried out from purification was Ethyl Acetate & n-Hexane. Chalcone derivatives (2a-k), malononitrile and anhydrous ammonium acetate were taken in RBF and absolute ethanol was used as solvent. This mixture was refluxed for 7-8 hours. Then cooled to RT. As solution attained RT, solid was obtained. Filtration & washing was done with dist. H_2O thoroughly, recrystallization from Ethanol to yielded compounds (3a-k)[23].

Compound (3a-k) and excess of glacial CH_3COOH were mixed and then refluxed condition for 7-8 hours. Glacial acetic acid was self-solvent. After the completion of reaction, solution was cooled to RT. Solid thus obtained, was filtered, then washed thoroughly with cold dist. H_2O several times, dried, Dioxane was used for recrystallization to give compounds (4a-k).

Various derivatives of 3-(2-Chloroacetyl)-5-(2,4-substitutedphenyl)-2-Methyl-7-(2-Oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d]Pyrimidin-4(3*H*)-one (5a-k) were synthesized from compounds (4a-j). Saturated solution of sodium acetate was prepared in glacial acetic acid. Compound (4a-k) was dissolved drop wise to the mixture and then was cooled at 0-5°C. Chloroacetyl chloride was dropwise added in the solution at 0-5°C during 1 h time period. When addition was completed, this reaction mixture was heated at 80°C for 1.5 h & this solution was stirred at RT for 12 h which gave compounds (5a-k).

Various derivatives of N-(Hydroxy-adamantan-1-yl)-5-(2,4-substituted phenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2*H*-Chromen-3-yl) Pyrido[2,3-d]Pyrimidine-3(4*H*) carboxamide (6a-k) were synthesized by reaction between the mixture of 3-aminoadamantan-1-ol and K_2CO_3. This was refluxed for 5-6 h and then the solution was cooled to RT. Then this mixture was dumped into ice to obtain solid, which was filtered & washed with distilled water, dried and finally recrystallization was carried out using Ethanol to yield (6a-k) products.

The compounds were confirmed by study of FT-IR spectra, using KBr discs. on Perkin-Elmer 1600 FTIR, ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker 500 MHz in DMSO-d_6 as solvent was used and TMS–tetra methyl silane was internal standard respectively. LC-MS were carried out on LCMS. According to NMR data presence of methyl group showed value of δ near 2.92-3.09, proton of the secondary of NH group showed value of δ near 6.76-7.35, -OH group pf adamantane showed value of δ near 3.43-3.47, -OCH_3 showed value of δ near 3.79-3.90 and 5H of coumarin showed value of δ 6.75-8.59. Fig. 1 to 4 shows ^{1}H NMR spectra of the compounds TT_1, TT_3, TT_5 and TT_8 respectively. Fig. 5 shows ^{13}C NMR spectra of the compound TT_1. Fig. 6 and 7 shows IR spectra of the compounds TT_1 and TT_3 respectively. Fig. 8 represents LCMS spectra of the compounds TT_1 and TT_3 respectively.

Biological activity

Antibacterial activity: Table 3 shows MIC (minimum inhibition concentration) of the N-(3-Hydroxyadamantan-1-yl)-5 -(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2*H*-Chromen-3-yl) Pyrido[2,3-d]Pyrimidine-3(4*H*)Carboxamide (6a-k) (Graph-1). Majority of the molecules which were tested, showed noticeable activities against *E. coli, P.aeruginosa, S.aureus* & *S.pyogenes*. From the results of antibacterial study of these *N*-(Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*)carboxamide (6a-k) derivatives such as TT_1 (R_1= -H and R_2= -OCH_3), TT_6 (R_1= -H and R_2= -Br), TT_8 (R_1= -H and R_2= -CH_3) and TT_9 (R_1 = -Cl and R_2= -Cl) showed better activity at 50 µg/mL; TT_3 (R_1=

-H and R_2=$(CH_3)_2$N-) and TT_{10} (R_1= -Br and R_2= -H) showed better activity at 62.5 µg/mL; TT_2 (R_1= -H and R_2= -Cl), TT_4 (R_1= -H and R_2= -OH), TT5 (R_1= -H and R_2= -NO_2), TT_7 (R_1= -OH and R_2= -H) and TT_{11} (R_1= -Br and R_2= -H) showed better activity at 100 µg/mL against *E. coli* as comparing with Ampicillin (MIC=100 µg/mL).

N-(Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2H-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*) Carboxamide (6a-k) derivatives such as TT_3 (R_1= -H and R_2=$(CH_3)_2$N-) showed better activity at 50 µg/mL; TT_1 (R_1= -H and R_2= -OCH_3) and TT_8 (R_1= -H and R_2 = -CH_3) showed better activity at 62.5 µg/mL; TT_2 (R_1= -H and R_2= -Cl), TT_6 (R_1= -H and R_2= -Br), TT_9 (R_1= -Cl and R_2= -Cl) and TT_{10} (R_1= -CH_3 and R_2= -H) showed better activity at 100 µg/mL against *P. aeruginosa* as comparing with Ampicillin (MIC= 100 µg/mL) and equivalent as Chloramphenicol (MIC=50 µg/mL).

N-(Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2H-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*) Carboxamide (6a-k) derivatives such as TT_9 (R_1= -Cl and R_2= -Cl) showed better activity at 50 µg/mL; TT_1 (R_1= -H and R_2= -OCH_3), TT_4 (R_1= -H and R_2= -OH), TT_{10} (R_1= -Br and R_2= -H) and TT_{11} (R_1= -Br and R_2= -H) showed better activity at 100 µg/mL against *S. aureus* as comparing with Ampicillin (MIC = 100 µg/mL) and *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2H-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*) Carboxamide (6a-k) derivatives such as TT_1 (R_1= -H and R_2= -OCH_3), TT_2 (R_1= -H and R_2= -Cl) and TT_8 (R_1= -H and R_2= -CH_3) showed better activity at 62.5 µg/mL; TT_3 (R_1= -H and R_2=$(CH_3)_2$N-), TT_9 (R_1= -Cl and R_2= -Cl) and TT_{10} (R_1= -Br and R_2= -H) showed better activity at 100 µg/mL against *S. pyogenes* as compared to Ampicillin (MIC=100 µg/mL).

Antifungal activity

The minimum inhibition concentration of the *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-oxo-7-(2-Oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d] Pyrimidine-3(4*H*) Carboxamide (6a-k) is shown in Table 4 (Graph-2). Most of the compounds tested, exhibited considerable activities against *C. albicans*, *A. niger* & *A. clavatus*. Antifungal activity results of *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2*H*-Chromen-3-yl) Pyrido[2,3-d]Pyrimidine-3(4*H*)-Carboxamide (6a-k) derivative such as TT_2 (R_1= -H and R_2= -Cl) and TT_6 (R_1 = -H and R_2= -Br) showed better activity at 50 µg/mL; TT_5 (R_1= -H and R_2= -NO_2) and TT_8 (R_1 = -H and R_2= -CH_3) showed better activity at 62.5 µg/mL; TT_1 (R_1= -H and R_2= -OCH_3), TT_4 (R_1= -H and R_2= -OH), TT_7 (R_1= -OH and R_2= -H) and TT_{11} (R_1= -Br and R_2= -H) showed better activity at 100 µg/mL against *C. albicans* as compared Nystatin (MIC=100 µg/mL) and Griseofulvin (MIC=500 µg/mL). *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3-(4*H*)-Carboxamide (6a-k) derivative such as TT_5 (R_1= -H and R^2= -NO_2) better activity at 50 µg/mL; TT_2 (R_1= -H and R_2= -Cl) showed better activity at 62.5 µg/mL; TT_1 (R_1 = -H and R_2 = -OCH_3), TT_3 (R_1= -H and R_2= $(CH_3)_2$N-), TT_4 (R_1= -H and R_2= -OH), TT_6 (R_1= -H and R_2= -Br), TT_7 (R_1= -OH and R_2= -H) and TT_{11} (R_1= -Br and R_2= -H) showed better activity at 100 µg/mL against *A. niger* as comparing with Nystatin (MIC=100 µg/mL) and Griseofulvin (MIC=500 µg/mL). *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*)-Carboxamide (6a-k) derivative such as TT_1 (R_1= -H and R_2= -OCH_3) and TT_8 (R_1= -H and R_2= -CH_3) showed better activity at 50 µg/mL; TT_5 (R_1= -H and R_2= -NO_2) better activity at 62.5 µg/mL; TT_2 (R_1= -H and R_2= -Cl), TT_6 (R_1 = -H and R_2= -Br), TT_{10} (R_1= -Br and R_2= -H) and TT_{11} (R_1 = -Br and R_2 = -H) showed better activity at 100 µg/mL against *A. clavatus* as comparing with Nystatin (MIC=100 µg/mL) and Griseofulvin (MIC=500 µg/mL).

Anti tubercular activity

Very promising results of antibacterial activity test of N-3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-(2-Oxo-2H-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*) Carboxamide (6a-k) directed to study out more primary screening against *M. tuberculosis*. The antitubercular activity results of Pyrido[2,3-d] Pyrimidine derivatives (6a-k) presented in Table 4 (Graph-3). For the screening trials, concentration of exhibiting compounds was 1000, 500 and 250 µg/mL. From these, the compounds exhibiting good activity in the primary screening were considered for secondary screening against *M. tuberculosis* H_{37}RV in the L. J. Medium. The results of the antitubercular activity were matched with Rifampicin at the concentration 40 µg/mL. *N*-(3-Hydroxyadamantan-1-yl)-5-(2,4-substitutedphenyl)-2-Methyl-4-Oxo-7-

(2-Oxo-2*H*-Chromen-3-yl)Pyrido[2,3-d]Pyrimidine-3(4*H*) carboxamide (6a-k) such as TT_1, TT_7 and TT_{11} containing bromo, hydroxy and methoxy substituted derivatives exhibited *M. tuberculosis* MIC values in around 62.5 µg/mL producing 95-99% better results. But the other compounds exhibited moderate to poor activity against *M. tuberculosis* $H_{37}RV$.

Anti malarial activity

Antimalarial activity of Pyrido[2,3-d] Pyrimidine derivatives (6a-k) is shown in Table 5. Chloroquine and Quinine were the standard drugs used to compare antimalarial activity. The values of MIC are 0.020 µg/mL and 0.268 µg/mL respectively. Pyrido[2,3-d]Pyrimidine derivatives no. 1 & 2, 4 to 11 showed better activity at 0.88 µg/mL, 0.25 µg/mL, 0.98 µg/mL, 0.74 µg/mL, 0.42 µg/mL, 0.35 µg/mL, 0.46 µg/mL, 0.31 µg/mL, 0.52 µg/mL and 0.23 µg/mL respectively as antimalarial activity comparing with to Quinine (MIC=0.268 µg/mL).

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