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Synthesis some pyrimidine derivative of thymidine compound

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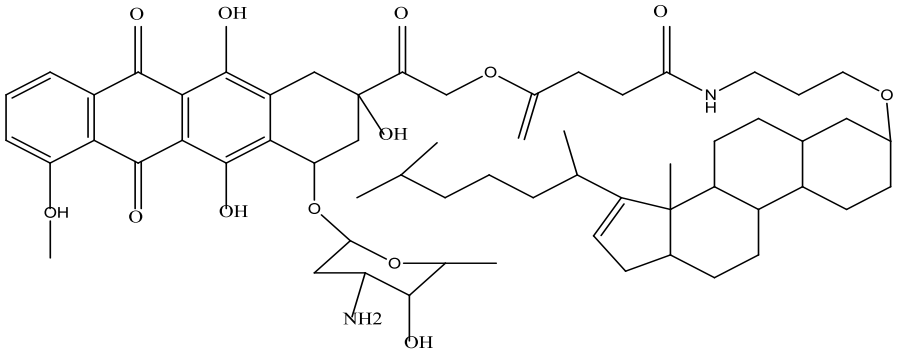
Abstract
Pyrimidine is the aromatic heterocyclic organic compound. It has the three diazines, six membered heterocyclic with two nitrogen atom in the ring & also have nitrogen atoms in the positions 1 or 3 in the ring and also present in the nucleic acids, three types of the nucleobases derivatives cytosine (C), Thymine (T), & Uracil (U).
In this article we explore the synthesis of drug Doxorubicin, Galanthamine, Narwedine, Haementadine & (Z)-& (E)-2,2 [Bis (hydroxymethyl) cyclopropylidene] methylpurins & Pyrimidine.
Also describe the anticancer activity of some doxorubicin derivatives because the doxorubicin derivative shows anticancer activity.
Thymidine ring also show the anticancer activity so we choose the both of the ring & also check the anticancer activity.

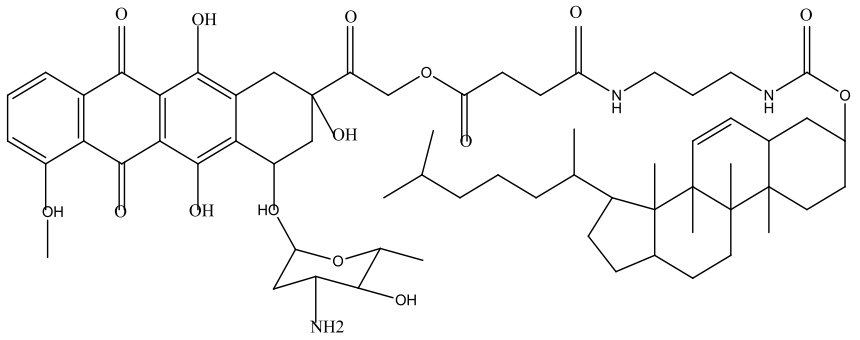
Keywords: (Z) - and (E)-2, 2 [Bis (hydroxymethyl) cyclopropylidene] methylpurins and –pyrimidine, doxorubicin, galanthamine, narwedine, haementadine

Introduction
Today, heterocyclic compound are the major resource of every compound & majority of the compound synthesized by the heterocyclic compound only. The alkaloid pyrimidine was synthesized by benzophenone mediated photo induced coupling between saturated heterocyclic & sulphonylpyrimidines [29] In DNA & RNA, pyridine also have the basic nucleus. The derivatives of the pyrimidine also possess the anticonvulsant, antimicrobial, anti- inflammatory, antitumor, & antihistaminic activity [59].
Thymine contains the five bases nucleic acid along with adenine, guanine, cytosine & uracil. Thymine is the derivative of Pyrimidine that derived by the methylation of uracil at the 5th carbon. It is also a part of one of the most common mutation of the DNA that involve in the adjustment of thymines&cytocines. In the treatment of the cancer, its target for action of 5- fluorouracil (5-FU).

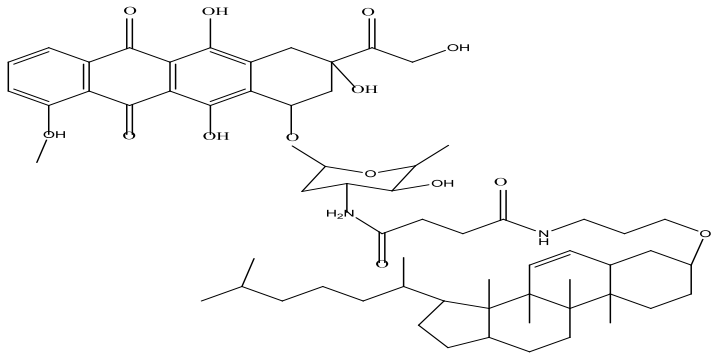
Synthesis of cholesterol Doxorubicin, its derivative & their anticancer activity
An anthracycline agent doxorubicin produced by fungus *Streptomyces peucetius*, which is used for treatment of cancers specially in leukaemia, Brest& ovarian carcinoma [2, 3]. Dox are inhibit topoisomerase 2, intercalates into DNA strand, that require for maintaining DNA replication [4, 5]. In dox rapid distribution, excretion, & low bioavailability done by highly hydrophilic nature, distribution & short half-life [6, 7].



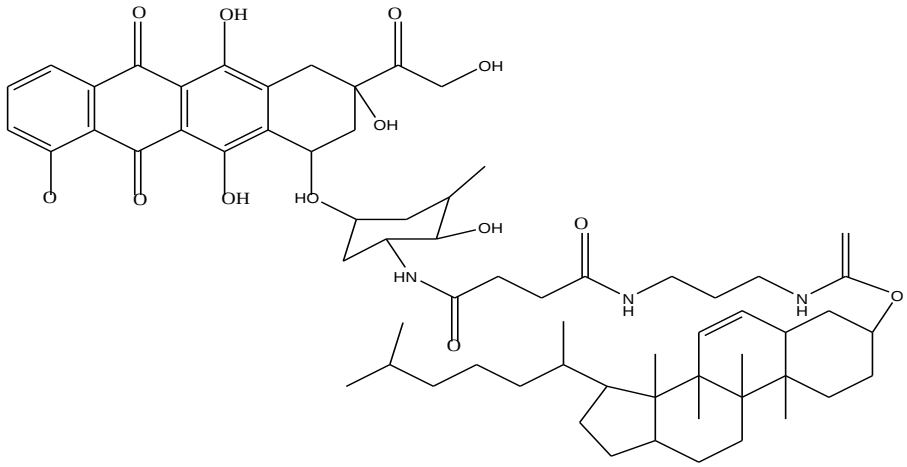
LIPO DOX 1



LIPO DOX 2



LIPO DOX 3



LIPO DOX 4

Fig 1: Class of dox derivatives.Lipo-dox 1 and lipo-dox 2 were linked between doxorubicin hemisuccinate and lipid by amide bond, lipo-dox3 and lipo-dox 4 were linked by ester bond.

The functional group of dox are (-OH, -NH_2) available for chemical modification & its derivative are

1. One substituent at alcohol group of hydroxyl acetyl part in anthracycline ring (lipo- dox 1, lipo- dox 2).
2. Substitution at amino group in amino sugar part (lipo-dox 3, lipo-dox 4).

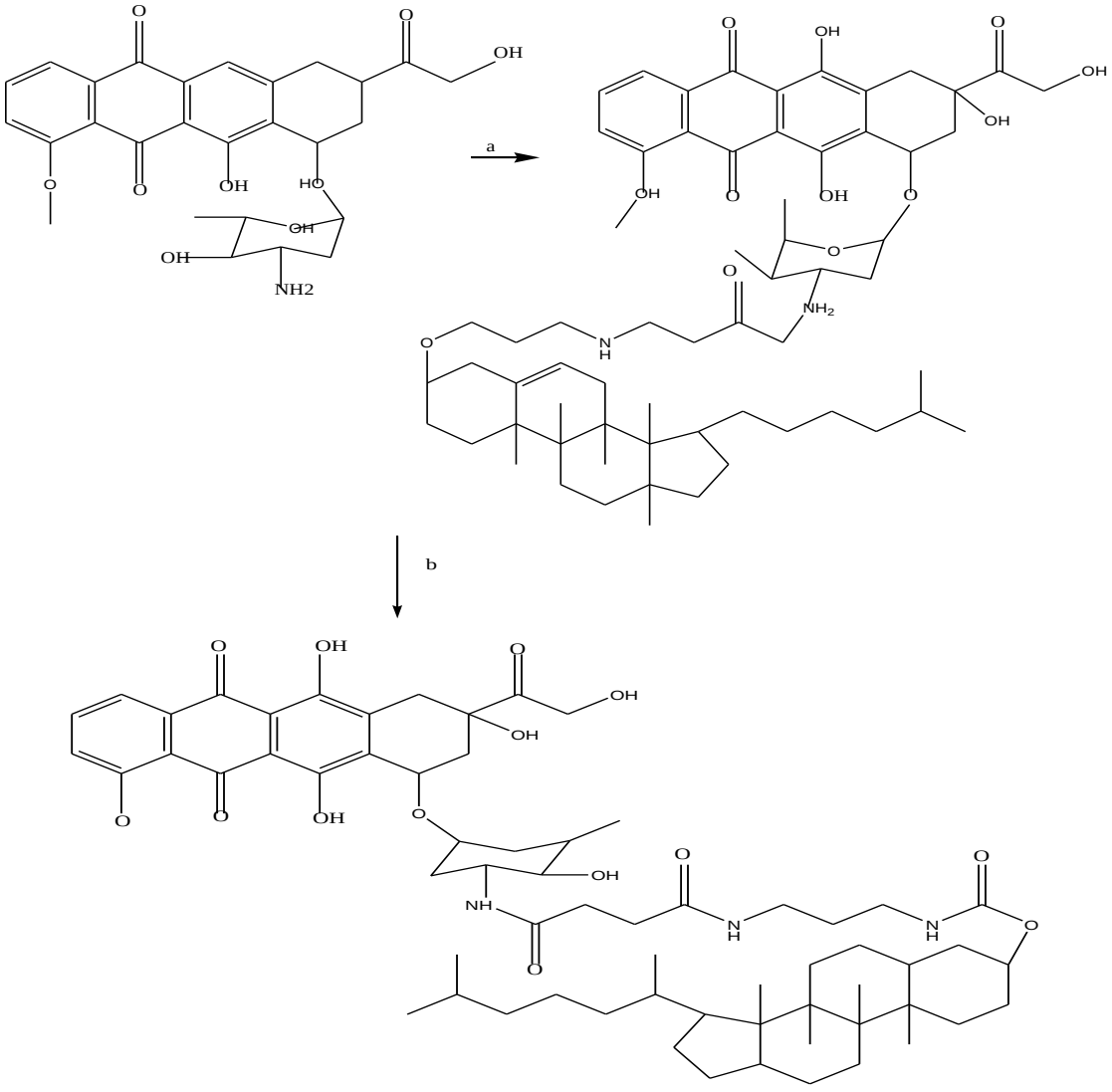
Scheme 1: Synthesis of lipo-dox A and lipo-dox B. Reaction conditions: (a) FmocOSu, DIPEA / CH_2Cl_2, DMF, 2 h, r.t, (yield: 80%); (b) succinic anhydride, TEA/CH_2Cl_2, DMF, 8 h,r.t. (yield: 71%); (c) lipid A, DIPEA, HBTU/CH_2Cl_2, DMF, 5 m, r.t. (yield: 85%); (d) lipid B, DIPEA, HBTU/CH_2Cl_2, DMF, 5 m, r.t, (yield: 75%); (e) piper dine, CH_2Cl_2, DMF, 10 m, r.t, (yield: 66%).

Doxorubicin (anticancer agent) have disadvantages such as rapid excretion, short retention time & cardio toxicity. It gives lipophilic property to dox, so doxorubicin modify with cholesterol derivative that were validated as a component of liposomal gene delivery.

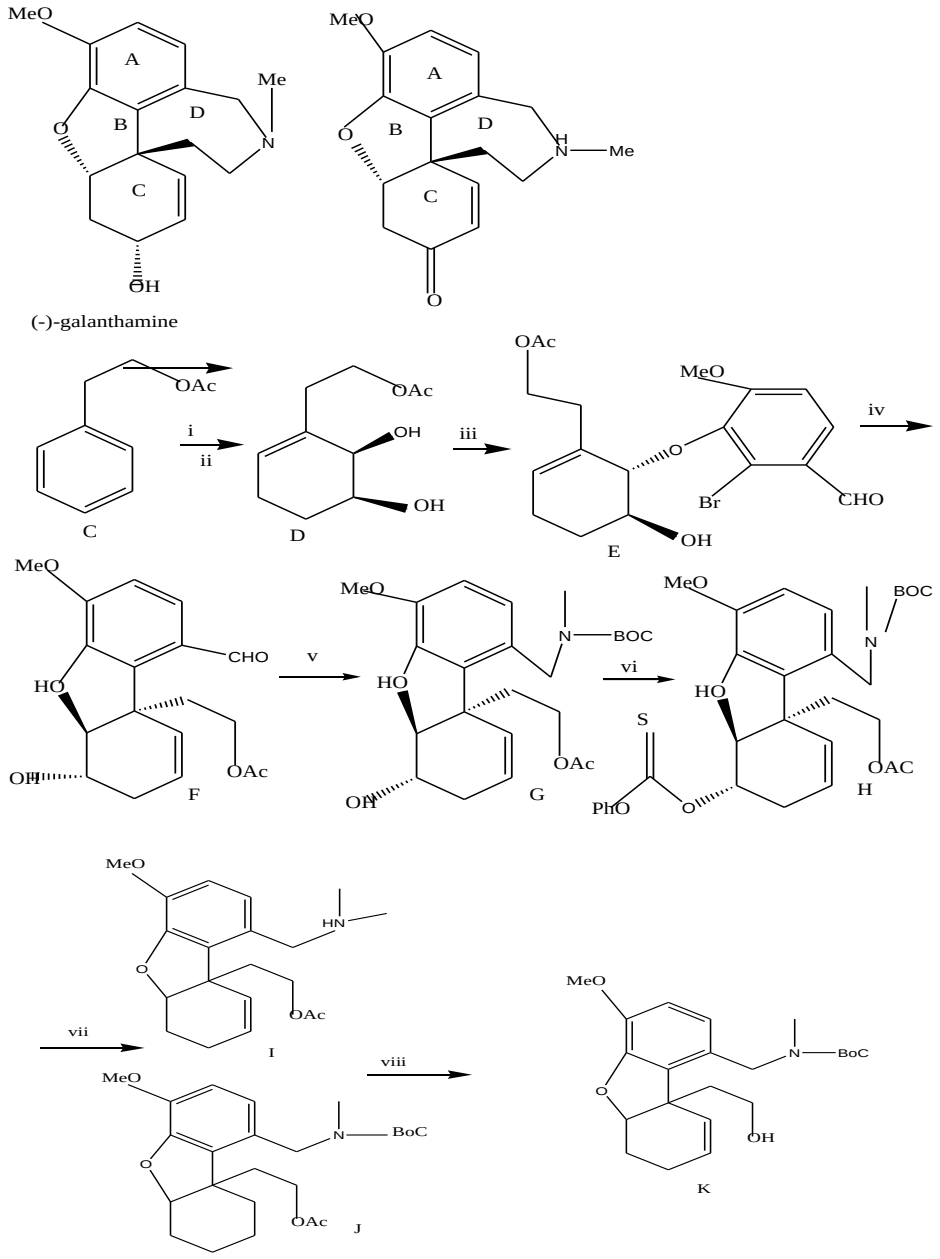
In the comparison to parent drug, the lipophilic property of liposomal dox 1 & liposomal dox 2 induced more accumulation in cells.

Fmoc group is necessary for protection because amine reactivity. NFmoc- dox (compound A) synthesized by dox, 9

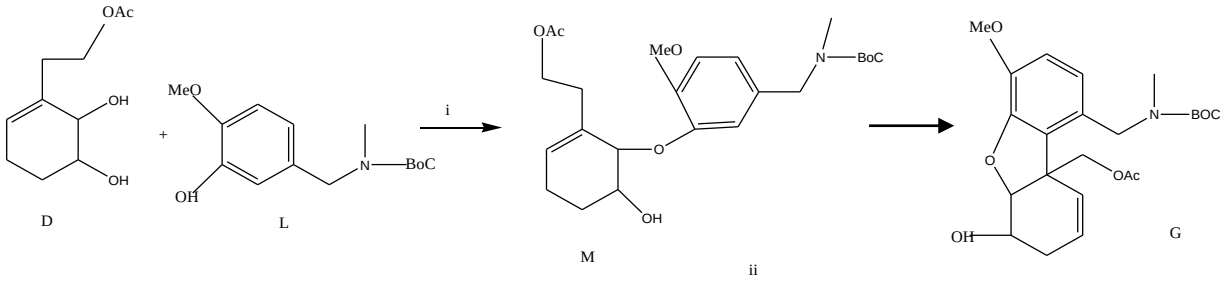
fluorenyl methyl succinimidyl carbonate (Fmoc – O – su), diisopropyl ethyl amine (DIPEA) in CH_2Cl_2/DMF (90/10, v/v) for 2 hr. Observation of the reaction done by TLC & purification also done by silica gel chromatography. In this reaction Nfmocdox was elongated with succinic anhydride & DIPEA for 8 hr in CH_2Cl_2/DMF because of modification of cholesterol derivatives. By the help of the red powder, NFmocdoxhemisuccinate (compound B) was made. In the synthesis of the Nfmoclipo-dox 1 & lipo-dox 2 (compound C,D), cationic lipid- lipid A, lipid B, were added while stirring with compound B, DIPEA, HBTU for several minute. In the final stage, by the help of de- protection step with piperidine in CH_2Cl_2/DMF lipo-dox 1 &lipo-dox 2 (Compound D, F) were obtained as red powder. Other compounds like lipo-dox 3 &lipo-dox 4 was synthesized by one – pot two step reaction, because hemisuccinate was unstable & difficult to purify. DIPEA is add to dox, succinyl anhydride in CH_2Cl_2/DMF (90/10, v/v).In some case, DIPEA is added to solution for few more minute when TLC spot was moving upper during the reaction, cationic lipids. Then washing it with 0.1% TFA water & purifying with C 18, silica gel chromatography, compounds G, H were obtained as red powder. By the help of NMR, MALDI-TOF, & HPLC Key compound were conformed.



Synthesis of Galanthamine & Narwedine



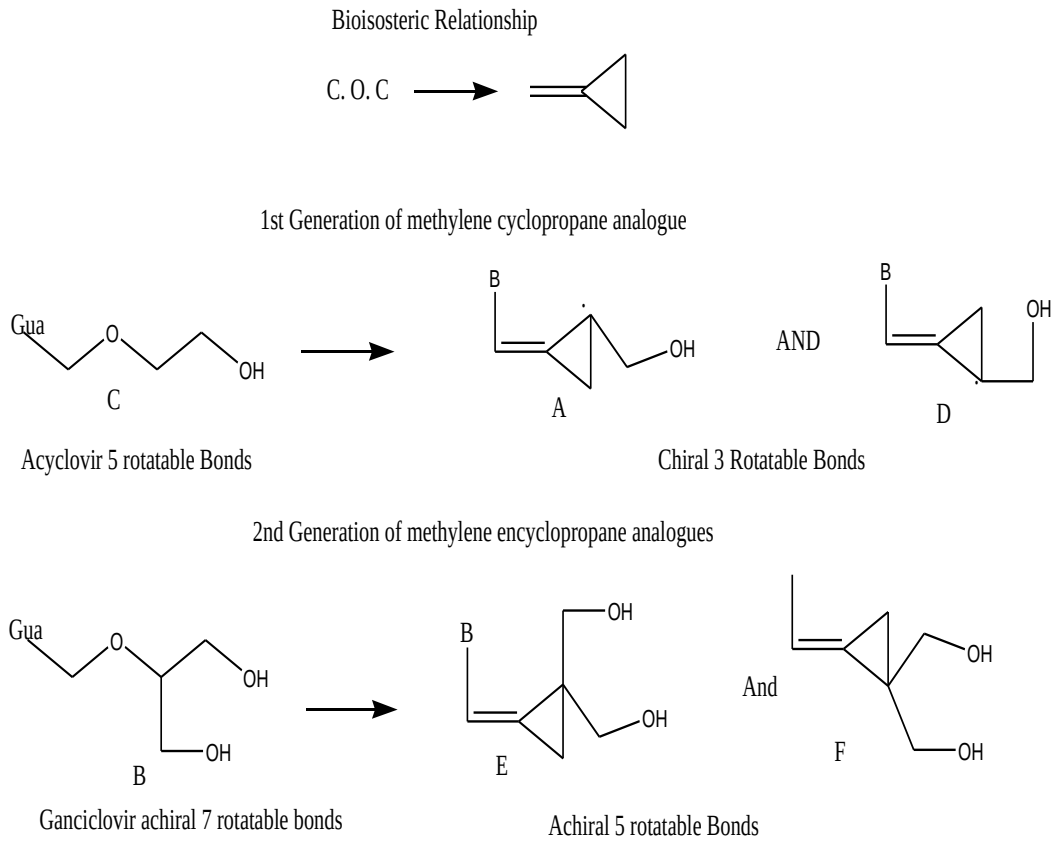
Scheme 2: Preparation of Intermediate **8**.i) *E. coli* JM 109 (pDTG601A), 80%; ii) PAD, MeOH, HOAc, 85%; iii) bromoisovanillin, Bu3P, TMAD, THF, 87%; iv) Ag2CO3, dppf, Pd(OAc)2, toluene, reflux, 87%; v) a. Ti(*i*PrO)4, NH2Me.HCl, NEt3, MeOH, b. NaBH4, c. Boc2O, NEt3, EtOH, 80%, ; vi) PhOCSCl, pyridine, DCM, 84%; vii) *n*-Bu3SnH, AICN, toluene, 80 °C, 60%; viii. Aq. NaOH, MeOH, 89%.



Synthesis and Antiviral Activity of (Z)- and (E)-2,2 [Bis(hydroxymethyl)cyclopropylidene]methylpurines and -pyrimidines: Second-Generation Methylenecyclopropane Analogues of Nucleosides 1

In the preparation of the first generation analoguesA1-A4 & D1-D4, the alkylation- elimination procedure is useful [57]. In the scheme 4 the alkylating agent 1- bromo 1-bromomethyl-2,2bis – (acetoxymethyl) cyclopropane (G) is prepared. Reaction is available diethyl isopropylidenemalonate (H) with NBS & dibenzoyl peroxide in CCl_4 under illumination with light gave bromo derivative I as crud eproduct in quantitative yield. By the using of tBuOK in tBuOH, the compound I is transferred toa 1:1 mixture of diethyl isopropylidenemalonate (H) & diethyl methylenecyclopropane 2, 2 dicarboxylate J (47%) [58]. The starting bromo ester I is free from isopropylidenemalonate H. The transfer of positive bromine from I to reagent or solvent, the diester H is formed.

Scheme 3



Series a :B = adenine,

Series b: B = guanine

Series c: B = Cytocine

Series d : B = Thymine

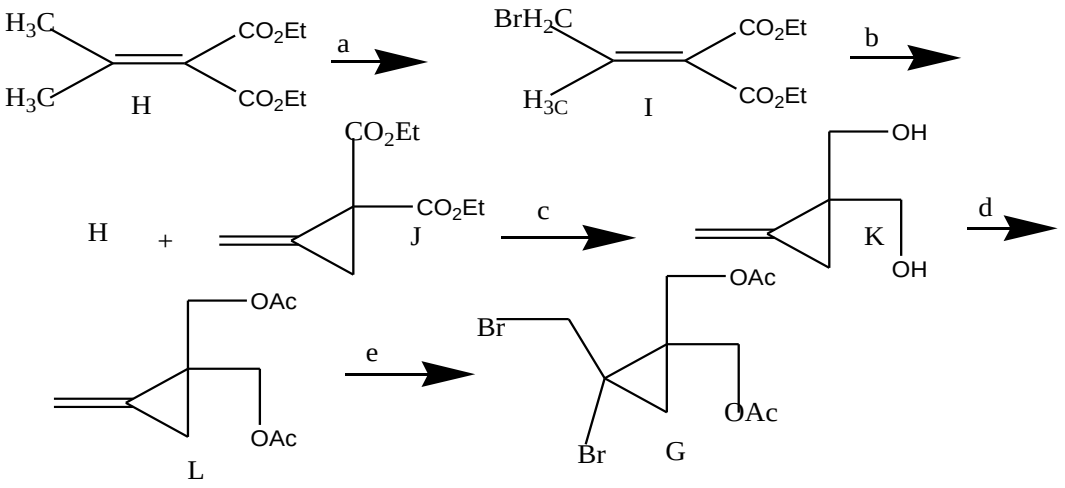
Series e : B = 2- amino 6- cyclopropylaminopurine

Series f:B = 2- amino 6- chloropurine

Series g : B = 2- amino 6 methyl purine

Series h: B = 2,6 - Diamino purine

Series i : B = 2- amino 6- fluropurine

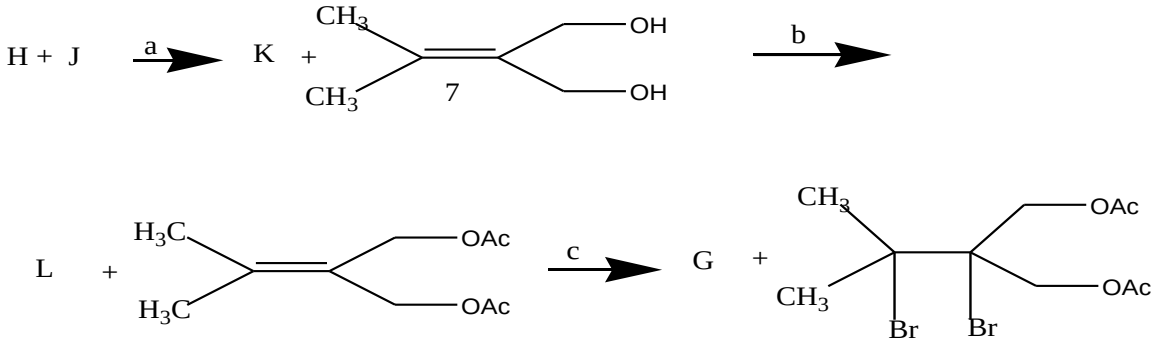


(a) NBS, $(BzO)_2$,CCl_4, illumination. (b) (1) t-BuOK, TBuOH,
(2) Seperation. (c) $LiAlH_4$, Et_2O. (d) Ac_2O, pyridine. (e) Br_2, CCl_4

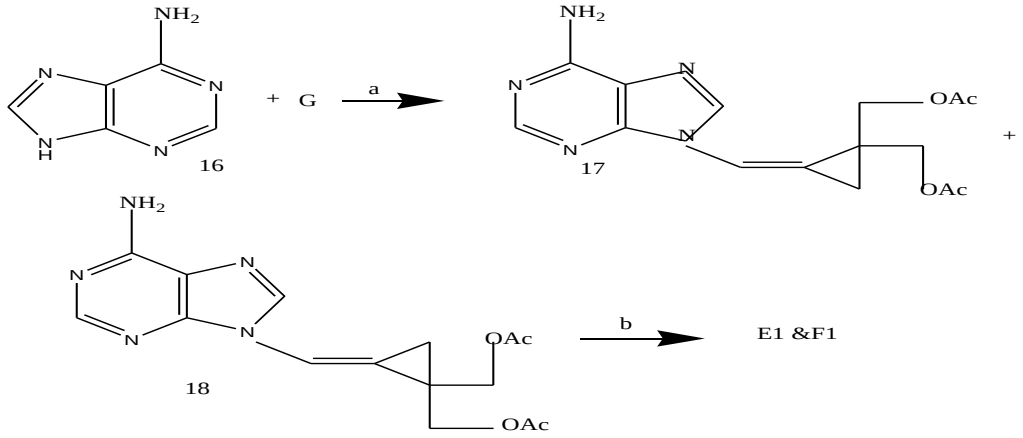
Scheme - 4

In the description of the nucleoside analogues A1- A4, which combine a methyllenecyclopropanesystem [51]. In the vitro against a broad spectrum of DNA viruses, especially in the human cytomegalovirus (HCMV) & Epstein – Barr virus (EBV), the Z- isomers of these analogues have effective [52-53]. In vivo against Balb/c mice infected with murine CMV, the analog of synguanol (A1) & 6- cyclopropylamino are orally effective [54]. The clinical isolates of HCMV including resistant to ganciclovir& laboratory, the analogues A1 & A5 are effective against [55, 56].

Scheme -5

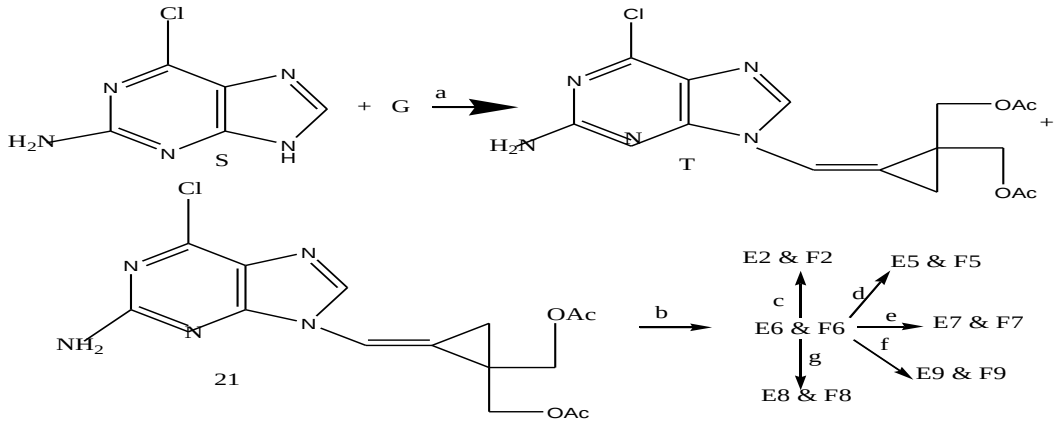


(a) $LiAlH_4$, Et_2O. (b) AC_2O, Pyridine. (c) (1) Pyridine.HBr_3, CH_2Cl_2: (2) seperation.



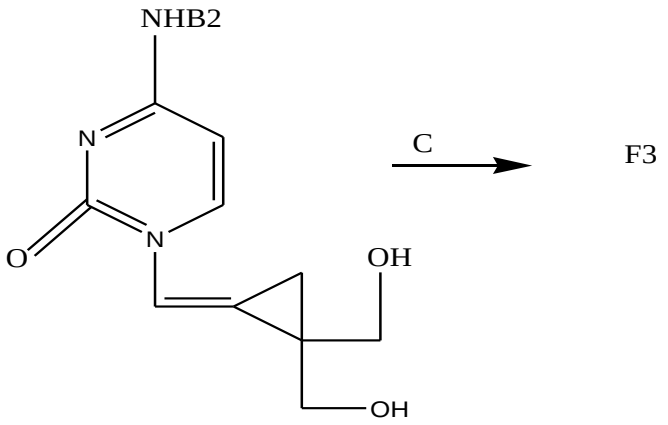
(a) k_2CO_3, DMF (b) (1) K_2CO_3, $MeOH/H_2O$; (2) seperation.

Scheme-6



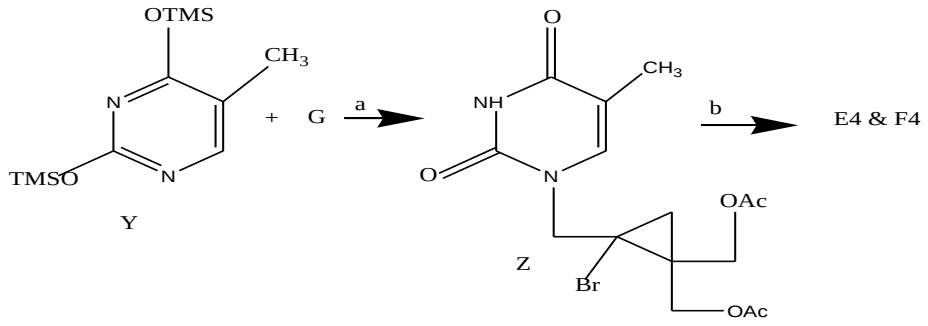
(a) K_2CO_3,DMF, (b) (1) K_2CO_3, MeOH/H_2o, (2) seperation.
(c) (1) HCO_2H (2) NH_3, MeOH. (D) cyclopropylamine, EtOH.
(e) K_2CO_3, MeOH. (f) KF, catalytic NMe_3, DMF. (g) NH_3, MeOh

Scheme 7



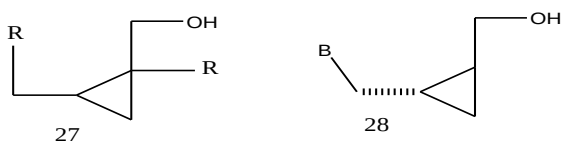
A. 1) K2CO3,DMF 2) MeOH B. 1) BZ2O, EtOH, 2) Seperation C. NH3, MeOH.

Scheme 8



a. MeCN,

b. 1. K_2CO_3,DMF, then MeOH, 2. Seperation.



27a:R = H

27b: R= CH_2OH

B = nucleic acid base

(a) MeCN, (b) (1) K_2CO_3, DMF, then MeOH, (2) separation.

The source of bromoniumcation, diethyl bromomethylmalonate (vinylogue) is regarded as compound I [59].

Table 1: Comparison of Selected 1H NMR Chemical Shifts (δ) of the Z-Isomers E1-E4 and A1-A4 with E-Isomers F1-F4 and D1-D4

Isomer[a]	OH	H_1	H_8 OR[B] H_6	H_5	H_{51}
A1 (26)	5.11	7.38	8.74	3.33, 3.73	0.40
E1 (26)	5.07	7.37	8.82	3.52, 3.68 3.53, 3.67	0.16 0.14
D1 (5)	4.82	7.48	8.48	3.41	-
F1 (5)	4.76	7.48	8.49	3.46, 3.52 3.53, 3.67	0.06 0.03
A2 (26)	5.04	7.11	8.31	3.41	0.36
E2 (26)	4.99	7.07	8.41	3.46, 3.52 3.48, 3.51	0.15 0.13
D2 (5)	4.80	7.21	8.04	3.32, 3.68	-
F2 (5)	4.76	7.21	8.03	3.41, 3.48 3.43, 3.47	0.07 0.04
A3 (26)	4.93	7.30	8.13	3.31, 3.53	0.22
E3 (26)	5.02	7.31	8.27	3.34, 3.57	0.23
D3 (5)	4.75	7.37	7.96	3.32	-
F3 (5)	4.78	7.38	7.96	3.37, 3.42 3.37, 3.41	0.05 0.04
A4 (26)	5.06	7.15	8.20	3.15, 3.71	0.56
E4 (26)	4.99	7.17	8.32	3.40, 3.60 3.41, 3.60	0.21 0.19
D4 (5)	4.75	7.22	7.81	3.32	-
F4 (5)	4.66	7.25	7.82	3.38, 3.45 3.40, 3.43	0.07 0.03

a All spectra were determined in CD3SOCD3. The δ values for A1, A2, D1, and D2 were taken from ref 3 and those for A3, A4, D3, and D4 from ref 4. The δ values of H5′ for compounds A1-A4 and D1-D4 reflect the centers of multiplets, whereas those for analogues E1-E4 and F1-F4were calculated from the respective AB spin systems. 17 b H8 of purines, H6 of pyrimidines.

Table 2: Inhibition of Human and Murine Cytomegalovirus (HCMV and MCMV) Replication by 2, 2-Bis(hydroxymethyl) methylenecyclopropane Analogues

Compound	EC_{50}/CC_{50}(μM)		
	HCMV/HFF[a]		
	TOMNE[b]	AD169[c]	MCMV/MEF[a]
E1	3.6/100	11.7/>404	9.7/>404
F1	>100/>100	>404/>404	NT[E]
E2	0.46/>100	0.49/>380	0.27/>380
F2	39/>100	123/>380	42/>380
E3	32/>100	14.3/>448	54/>448
F3	>100/>100	>448/>448	NT
E4	>100/>100	>420/>420	NT
F4	>100/>100	>420/>420	NT
E5	>100/>100	255/>331	NT
F5	>100/>100	327/>331	NT
E6	>100/>100	>355/>355	NT
F6	>100/>100	>355/>331	NT
E7	3.5/>100	2.7/>361	2.0/>361
F7	>100/>100	>361/>361	NT
E8	15/>100	>381/>381	NT
F8	>100/>100	313/>381	NT
E9	38/>100	22.2/>377	8.7/>377
F9	33/>100	43.7/>377	18.9/176
ganciclovir	4.1/>100	2.3/>392	5.0/>35

a Plaque reduction assay. b Visual cytotoxicity. cCytotoxicity by neutral red uptake. dCytopathic effect (CPE) inhibition assay. eNT) not tested

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