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Novel Synthesis Approach and Antiplatelet Activity Evaluation of 6-Arylmethyleneamino-2-Alkylsulfonylpyrimidin-4(3*H*)-one Derivatives and Its Nucleosides

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ABSTRACT

A new and efficient procedure has been designed for the preparation of 6-arylmethylene-amino-2-alkyl sulfonyl-pyrimidine. The first alkylthio group was introduced into the pyrimidine ring by *S*-alkylation. The introduction of the second one was successfully achieved using the phosphorous oxychloride method to afford 4-chloro-2-alkylthio-pyrimidines. Subsequent nucleophilic displacement by the corresponding alkylamines followed by glycoside bromide addition conveniently gave a series of the target compounds. Thus, the two same or different alkylamino groups were easily introduced into the pyrimidine ring through the two different approaches. The human anti-platelet aggregation activity of the newly synthesized compounds was also described.

Keywords: Natural Asset; Financial Value; Neural Network

1. Introduction

Pyrimidines play an essential role in several biological processes and have considerable chemical and pharmacological importance in terms that the pyrimidine ring can be found in nucleoside antibiotics, anti-bacterial and cardiovascular [1-9]. Pyrimidine derivatives, especially alkylthio-substituted pyrimidines [10], and thieno pyrimidines [11], have attracted much attention because of their quite high anti-platelet aggregation activity as inhibitors for P2-receptor family. As related works, there have been active attempts to develop the antagonist of P2Y receptors (which mediate platelet aggregation induced by adenosine diphosphate, ADP) by employing adenine nucleotide derivatives containing two phosphate groups, *i.e.*, adenosine-3',5'-bis-phosphate analogues, as P2Y1 receptor antagonists [12,13] and 4-alkoxyl-2-alkylthio-6-aminopyrimidine derivatives as P2Y12 receptor antagonists [14]. The evaluated anti-platelet aggregation ability of a series of the synthesized pyrimidine derivatives proves their potential as lead compounds to develop a new series of P2Y12 antagonists [14]. Furthermore, the results appear to suggest the importance of the chemical structure of alkyl-thio-substituents and of the presence of a free amino group for the activity. As for adenine nucleotide analogues against P2T receptor, there's effective enhancement of the activity by N-mono-alkylation at the 6-position of the adenine moiety [15]. Considering such findings on the structure of the antagonist candidates, we achieved one hypothesis that N-monoalkylation of pyrimidine compounds might also increase anti-platelet aggregation activity. Furthermore, to date, there are few reports on the synthesis and evaluation of dialkyl(aryl) thio-substituted pyrimidines as platelet aggregation inhibitors. Hence, we designed to introduce another thio-nucloside group into the pyrimidine ring. As it is well known, the introduction of alkyl/arylthio groups into the pyrimidine ring is commonly achieved through either the alkylation of thiol groups or the nucleophilic substitution of halogens by alkylmer-captides. However, these processes must be conducted under harsh condi-

tions, especially in the absence of activating substituents. In the present study, we successfully introduced the two same or different alkyl amino groups into the pyrimidine ring, giving the intermediate 2- and 4-alkylamino pyrimidines. Thus far, there has been no report on the application of the diazotizatione-alkylthionation reaction to aminopyrimidine derivatives. The subsequent nucleophilic displacement of the chloro group in C-4-position by the corresponding amines affords a series of 4-alkylamino-2-thioxopyrimidines. Herein, we describe the details of the convenient synthesis and the evaluation results of all the synthesized compounds as human platelet aggregation inhibitors.

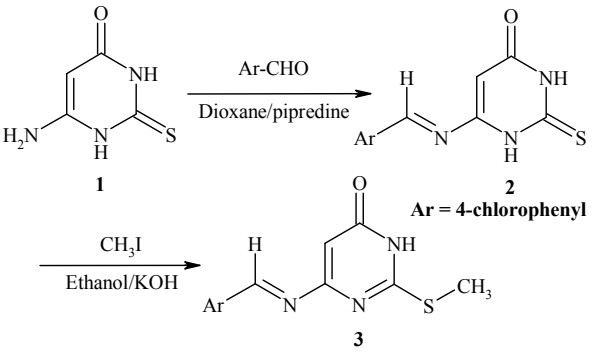
2. Results and Discussion

2.1. Chemistry

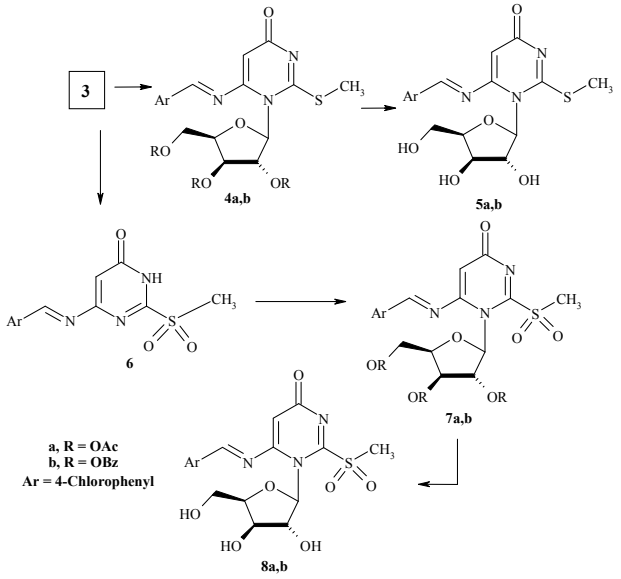
In a previous work we synthesized a series of substituted pyrimidines and substituted thieno[2,3-*d*] pyrimidine compounds [16,17] which presented a noticeable platelet antiaggregating power [18,19]. The most potent activity was exhibited by the thieno pyrimidinone derivatives. These thienopyrimidine compounds present a similar scaffold to the agents cited above. Several studies have shown that the presence of a quinazoline skeleton substituted in position 4 by vaious substituted anilino groups potentially increased the EGFR inhibitory effect [20,21]. According to the results observed with the former pyrimidine derivatives as platelet antiaggregating agents, the substitution of these compounds at the 4 position could lead to new PDGFR or EGFR pathway inhibitors. Our synthetic strategy to the final 2- and 4-alkylamino pyrimidine nucleosides was first to synthesize the glycosyl donor and then to condense with pyrimidine derivative bases. The pyrimidine bases were synthesized *via* the key intermediate **2** and **3** from 6-amino thiouracil and aromatic aldehydes followed by alkylation (**Scheme 1**).

The reactions of the starting 6-[(4-chlorophenyl)-meethylene]amino-2-methylthio-pyrimidin-4(1*H*)-one (**3)** with *β*-*D*-glycofuranosyl bromide were carried out in acetone in the presence of potassium carbonate under stirring at room temperature until the precipitation of sodium bromide had ceased. The reaction mixture was filtered off; the solvent was removed under reduced pressure, and the solid formed was purified by using flash chromatography afforded only one product in each case (as evidenced by TLC). The isolated products were identified as *N*-(2',3',5'-tri-*O*-acetyl/benzoyl-*β*-*D*-glycofuranosyl)-6-[4-(aryl)-methylene]amino-2-(methylthio) pyrimidin-4(1*H*)-one (**4a,b**). Deacetylation of the later nucleosides **4a,b** using saturated ammonia solution in methanol at room temperature afforded the corresponding deacetylated *N*-(*β*-*D*-glyco furanosyl)-6-{[4-(chlorophenyl)-methylene]amino}-2-(methylthio)-pyrimidin-4(1 *H*)-one (**5a,b**) respectively.

In the other way, the latter 6-[4-(chlorophenyl)-methylene]amino-2-(methylthio)pyrimidine series were oxidized in acetic acid solution containing hydrogen peroxide at room temperature, affording 6-[4-(chloro phenyl)-methylene]amino-2-(methylsulfonyl)pyrimidine (**6**). Under the same conditions [16] the condensation of 2-(methylsulfonyl)-pyrimidine (**6**) with *β*-*D*-glyco furanosyl bromide afforded N-(2',3',5'-tri-*O*-acetyl-*β*-*D*-glycofu-ranosyl)-6-[4-(chlorophenyl)methylene]amino-2-(me-thylsulf onyl)-pyrimidin-4(1*H*)-one (**7a,b**) which give respectively, the deacetylated *N*-(*β*-*D*-glycofurano syl)-6-[4-(chlorophenyl)-methylene]amino-2-(methylthio)-pyrimidin-4(1H)-one (**8a,b**), (**Scheme 2**). Some newer 6-[4-(aryl)-methylene]amino-2-alkyl-amino-pyrimidin-4(1*H*)-one, have been synthesized for the further diversification in our pyrimidine nucleosides core motif to generate alkylamino group at C-2 position via a two step protocol. The Fusion of 2-methythio- pyrimidine **3** with secondary alkyl amines namely (morpholine, piprazine and N-methyl piprazine) at 180˚C in sand bath without



Scheme 1. Synthesis the starting materials.

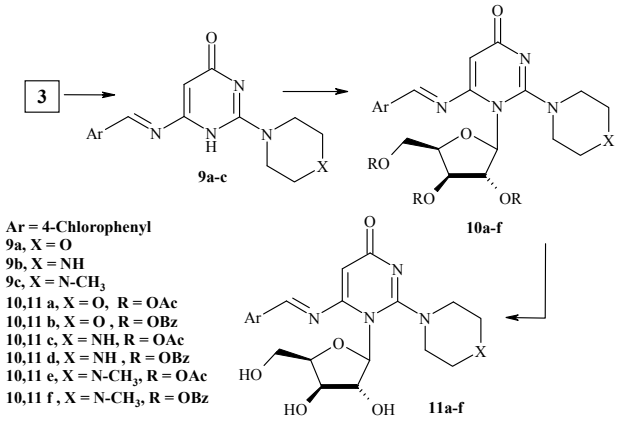


Scheme 2. Synthesis of Sulfone *N*-Nucleosides.

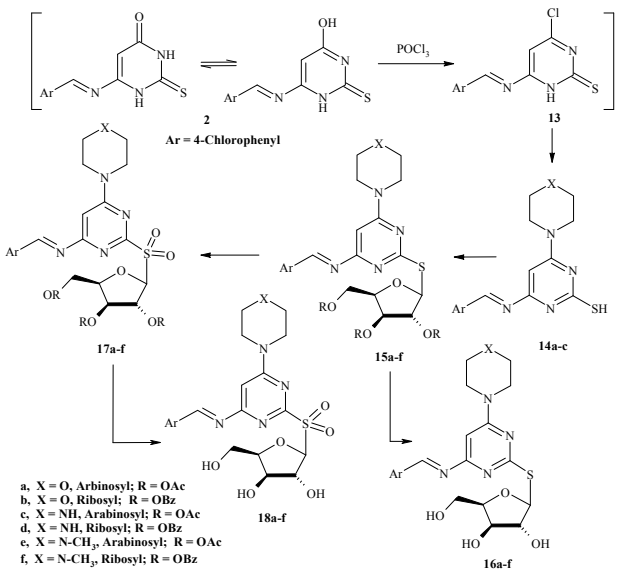
using any solvent, affording the 6-[4-(aryl)-methylene] amino-2-alkylamino-pyrimidin-4(1*H*)-one (**9a-c**), (**Scheme 3**). These lactol derivatives were transformed in to *N*-nucleosides derivatives (**11a-f**) by the reaction 2,3,5-tri-O-acetyl-*β*-*D*-glyco furanosyl bromide in quantitative yield.

Our recent interest was centered on the 4 position of pyrimidine nucleobases as potential anti-platelet agents. We modified the above mentioned uracils by introducing a alkylamino moiety and reported the synthesis of 4-(alka mino)-*N*-glycofuranosylpyrimidines **16a-f**, **18a-f** (**Scheme 4**) and studied there anti-platelet activity against. Thus, the phosphorus oxychloride in dry condition modified the pyrimidin-4-one (**2**) to 4-chloro pyrimidine (**13**), the latter is a key to introduced the alkyamino goups namely morpholine, piprazine, and N-methyl piprazine at 4-position in pyrimidines (**14a-c**), The synthesis was initiated by formation of potassium salts of the starting compounds **14a-c**. Potassium salt uracils reacted with protected sugar in the presence of acetone at room temperature to afford 4-alkyamino-pyrimidine acetylated *S*-nucleosides (**15a-f**) that were separated by flash colum chromate graphy in good yields. Treatment of glycosides **15a-f** with methanolic ammonia at room temperature afforded the nucleosides **16a-f**. Moreover, the acetylated *S*-nucleosides (**15a-f**) was oxidized in a mixture of acetic acid and hydrogen peroxide at room temperature affording the acetylated 6-[4-(aryl)-methylene]amino-2-(*N*-glycofuranosyl sulf one)-4-alkylamino-pyrimidine (**17a-f**), respectively in good yield (55% - 64%). Thin layer chromatography (chloro form: methanol, 8:2) indicated the formation of the pure compounds. The structures of **17a-f** were confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C.NMR) (cf. Exp.). The ^{1}H NMR spectrum of compound **17a** as an example, showed the anomeric proton of the glycoside moiety as a doublet at δ 6.81 ppm with a coupling constant $J_{1'-2'}$ = 3.69 Hz indicating *β*-configuration of the anomeric center. The other protons of the glycoside ring resonated at *δ* 4.00 - 5.40 ppm, while the three acetoxy groups appeared as three singlets at *δ* 1.94 - 2.15 ppm.

Deacetylation of acetylated nucleosides **17a-f** using saturated solution of ammonia in methanol at room temperature afforded the corresponding deacetylated nucleosides **18a-f** respectively. The structures of free nucleosides **18** have been established on the basis of their spectral data and elemental analyses. Thus, the ^{1}H NMR spectrum of **18a** showed the anomeric proton as a doublet at *δ* 6.84 ppm. The signals of the other five glycoside protons appeared at *δ* 3.94 - 5.73 ppm, while the signals that disappear on rapid exchange with D_2O are observed at *δ* 5.13. - 5.47 ppm, were assigned as the three hydroxyl groups.



Scheme 3. Synthesis of Nucleosides.



Scheme 4. Synthesis of sulfone *S*-Nucleosides.

2.2. Antiplatelet Aggregation Activity

The antiplatelet aggregation activity of the derivatives is listed in **Table 1**. All the tested derivatives effectively inhibited platelet aggregation higher than 50% at 100 μm concentration. The majority of the compounds showed lower IC50 values than that of aspirin and among them, compounds **18b**, **18d** and **18f** exhibited comparable IC_{50} values to that of indomethacin, a potent inhibitor of the enzyme COX. The results show that the tested compounds have a similar activity profile to those of previously studied pyrimidine derivatives, that is they inhibited AA-induced platelet aggregation more effectively than once ADP was used as inducer. However, compound **16f** showed satisfying activity with IC_{50} value of 18.1 μm against ADP-induced platelet aggregation; notably that this derivatives proved to be effective to inhibit platelet aggregation induced by both ADP and AA. Of the most potent derivatives, compounds **18f** and **18b** with IC50 values of 2.2 μm and 3.8 μm both contain five

Table 1. Antiplatelet activity evaluation of 2-/4-alkylamino-pyrimidine *S*- and *N*-nucleosides.

Compound No.	ADP		AA	
	Inhibition (%)[a,b]	IC_{50} (μm)	Inhibition (%)[b]	IC_{50} (μm)
5a	32.1	>100	99.8	84.9
5b	45.8	>100	99.9	18.3
8a	38.4	>100	100.3	21.4
8b	46.6	>100	100.0	79.8
11a	nd	nd	100.0	5.8
11b	60.1	81.92	99.7	7.3
11c	24.9	>100	100.0	63.4
11d	48.9	>100	99.9	15.5
11e	67.6	95.23	99.8	7.8
11f	49.7	>100	100.5	8.3
16a	38.3	>100	53.0	96.2
16b	2.4	>100	99.1	22.1
16c	34.1	>100	99.8	78.4
16d	49.2	>100	100.3	11.3
16e	3.7	>100	99.7	8.8
16f	81.3	18.1	103.0	21.1
18a	70.6	34.2	85.0	51.9
18b	33.4	>100	100.0	3.8
18c	3.1	>100	99.9	7.8
18d	29.7	>100	100.0	2.6
18e	1.9	>100	99.1	18.1
18f	34.8	>100	100.1	2.2
Indomethacin	42.2[c]	>100	100.0	3.0
Aspirin	21.4[c]	>100	99.8	30.3

five membered electron-rich heterocyclic rings and this would suggest that the existence of these ring systems can be an important factor affecting the antiplatelet activity. This has been confirmed the previous studies [22], as in their study the most potent derivative exerting dual inhibition of COX/LOX.7) Comparing the structures of this compound and compound **18b** shows that these two have a high extent of similarity; suggesting that they also may share common mechanisms of action and structure-activity relationships. This is also in line with the findings of Barreiro's group to discover some derivatives with furan substituent as potent inhibitors of AA induced platelet aggregation [23]. Of the synthesized derivatives, compound **16f** with dual inhibition of ADP/AA-induced platelet aggregation and compounds **18b-f** as the most active inhibitors of AA induced platelet aggregation have molecular weights ranging from 194 to 249 and *C* log*P* values ranging from 2.23 to 3.18. Therefore the mentioned derivatives have ideal physicochemical characteristics to be considered as starting points for further lead optimization studies in the area of antiplatelet aggregation drug research.

3. Conclusion

This paper describes a class of novel 2- and 4-alkylamino-pyrimidines and their nucleosides designed by considering the structural features of the previously reported derivatives proved to be bioactive inhibitor compounds. The derivatives were prepared by a one-pot procedure and evaluated for their antiplatelet aggregation activity using AA and ADP as aggregation inducers. The derivatives effectively inhibited platelet aggregation at

100 μm concentration and some of them exhibited inhibitory activities comparable to those of aspirin and indomethacin. Synthesis and study of antiplatelet activity of 2 and 4-substituted pyrimidine nucleosides will provide valuable information about the SAR of this group of compounds.

4. Experimental

4.1. Chemistry

Melting points were determined on the Electrothermal 9100 melting point apparatus (Electrothermal, UK) and are uncorrected. The IR spectra (KBr) were recorded on an FT-IR NEXCES spectrophotometer (Shimadzu, Japan). The ^{1}H NMR spectra were measured with a Jeol ECA 500 MHz (Japan) in DMSO-d_6 and chemical shifts were recorded in δ ppm relative to TMS. Mass spectra (EI) were run at 70 eV with a Finnigan SSQ 7000 spectrometer. The purity of the compounds was checked on Aluminium plates coated with silica gel (Merck). The elemental analysis for C, H, N and S was performed by a Costech model 4010 and the percentage values agreed with the proposed structures within ± 0.4% of the theoretical values. The Pharmacological evaluations of the products were carried out in Pharmacological Unit Pharmacology Department (NRC, Cairo, Egypt).

Synthesis of 6-[4-(chlorophenyl)methylene]amino-2,3-dihydropyrimidin-4(1*H*)-one (2). A mixture of 6-aminothiouracil 1 (10 m mol) and 4-chloro-benzaldehyde was refluxed in amixture of ethanol/piperdine (50 mL) for 5 hrs. (under TLC control), The reaction mixture was allowed to cool to room tempreature and then add water (100 mL), the precipitate was filtered off, dried and crystallized from dioxane (40 mL); as a pale yellow powder in 83% yield; m. p. 275˚C -277˚C, IR (cm^{-1}, ν): 3380 (br, NH), 1675 (CO); ^{1}H NMR: δ 3.42 (br, NH, D_2O exchangeable), 7.34 (d, J = 7.5 Hz, aryl-*H*), 7.97 (d, J = 7.5 Hz, aryl-*H*), 8.02 (s, pyrimidine-*H*), 8.36 (s, C*H*), 9.10 (br, NH); Its MS (m/z), 265 (M$^+$, 100%); $C_{11}H_8ClN_3OS$ (265.7).

Synthesis of 6-[(4-chlorophenyl)methylene]amino-2-methylthio-pyrimidin-4(1*H*)-one (3). To a warmed ethanolic KOH solution prepared by dissolving (10 mmol) of KOH in 50 mL (ethanol) was added each of compound 2 (10 mmol), the heating was continued for 30 min and the mixture was allowed to cool to room temperature, and the proper methyliodide (12 mmol) was added. The mixture was stirred under reflux for 5 h, then cool to room temperature, poured into cold water (100 mL). The solid product precipitated was filtered off washed with 100 mL water. The product was dried and crystallized from dioxane; as a white powder in 87% yield; m. p. 242˚C - 244˚C, IR (cm^{-1}, ν): 3376 (br, NH), 1682 (CO); ^{1}H NMR: δ 2.34 (s, SCH_3), 3.43 (br, N*H*), 7.34 (d, J = 7.5 Hz, aryl-*H*), 7.97 (d, J = 7.5 Hz, aryl-*H*), 8.19 (s, pyrimidine-*H*), 8.42 (s, C*H*); Its MS (m/z), 279 (M$^+$, 100%); $C_{12}H_{10}ClN_3OS$ (279.7).

Synthesis of 6-{[4-(chlorophenyl)methylene]amino}-2-(methylsulfonyl)-pyrimidin-4(1*H*)-one (6). The solution of 3 (0.01 mol) in hydrogen peroxide solution (30 ml) (AcOH, H_2O_2; 2:1) was stirred at room temperature for 10 hs. (under TLC control). The solvent was evaporated under reduced pressure at 90˚C, and the crude product collected, dried and crystallized from dimethyl formamide; as a white powder, in 76 % yield; m. p. 287˚C - 289˚C, IR (cm^{-1}, ν): 3365 (br, NH), 1680 (CO); ^{1}H NMR: δ 2.23 (s, SCH_3), 3.50 (br, NH, D_2O exchangeable), 7.34 (d, J = 7.46 Hz, aryl-*H*), 7.97 (d, J = 7.48 Hz, aryl-*H*), 8.11 (s, pyrimidine-*H*), 8.38 (s, C*H*); Its MS (m/z), 311 (M$^+$, 65%); $C_{12}H_{10}ClN_3O_3S$ (311.7).

Preparation of the acetylated *N*-nucleosides of 6-[4-(aryl)methylene]amino-pyrimidin-4(1*H*)-one (4a,b) and (7a,b); *General procedure*: To a solution of 3 or 6 (0.01 mol) in aqueous potassium hydroxide (0.01 mol) in distilled water (5 ml) was added a solution of 1-bromo-2,3,5-tri-*O*-acetyl-*α*-*D*-arabinofuranose/2,3,5-Tri-*O*-benzoyl-*β*-*D*-ribofuranosyl bromide (0.015 mol) in acetone (40 ml). The reaction mixture was stirred at room temperature for 18 - 24 h (under TLC control). The solvent was evaporated under reduced pressure at 40˚C, and the crude product was collected and washed with distilled water to remove KBr formed. The product was dried, and crystallized from dimethyl formamide (50 mL).

***N*-(2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(*methylthio*)-*pyrimidin*-4(1*H*)-*one* (4*a*).** It was obtained from 3 and 1-bromo-2,3,5-tri-O-acetyl-*α*-D-arabinofuranose; as white powder, m. p. 223˚C - 225˚C; IR (cm^{-1}, ν); 1710 (3CO), 1686 (CO); ^{1}H.NMR: δ 1.92, 1.98, 2.01 (3s, 3CH_3CO), 2.33 (s, SCH_3), 3.99 (m, H-4'), 4.12 (m, H-5', H-5''), 5.28 (m, H-3'), 5.35 (m, H-2'), 6.67 (d, J = 3.67 Hz, H-1'), 7.30 (d, J = 7.51 Hz, Ar-H), 7.97 (d, J = 7.50 Hz, Ar-H), 8.18 (s, pyrimidine-H), 8.45 (s, CH); ^{13}C. NMR: 21.43, 22.19, 22.24 (3CH_3), 28.32 (SCH_3), 60.59 (C-5'), 65.27 (C-3'), 66.87 (C-2'), 67.60 (C-4'), 86.60 (C-1'), 124.3-148.5 (10C-Ar), 166.8 (CO), 169.5, 170.9, 172.5 (3CO); Its MS (m/z), 537 (M$^+$, 38%); $C_{23}H_{24}ClN_3O_8S$ (537.9).

***N*-(2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(*methylthio*)-*pyrimidin*-4(1*H*)-*one* (4*b*).** It was obtained from 3 and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as pale yellow powder, m. p. 289˚C - 291˚C; IR (cm^{-1}, ν); 1720 (3CO), 1682 (CO); ^{1}H.NMR: δ 2.26 (SCH_3), 4.79 (m, H-4'), 4.62 (m, H-5', H-5''), 4.99 (d, J = 4.0 Hz, H-2'), 5.87 (t, J = 5.3 Hz, H-3'), 6.58 (d, J = 4.8 Hz, H-1'), 7.13 (m, Ar-H), 8.13 (m, 19H, Ar-H), 8.36 (s, pyrimidine-H), 8.72 (s, CH); ^{13}C. NMR: 21.16 (CH_3), 61.78 (C-5'),

65.69 (C-3'), 66.84 (C-2'), 67.38 (C-4'), 85.69 (C-1'), 121.157.6 (25C-Ar), 167.5 (CO), 170.3, 171.5, 173.6 (3CO); Its MS (m/z), 724 (M^+, 19%); $C_{38}H_{30}N_3O_8S$ (724.1).

***N*-(2',3',5'-*tri*-*O*-*acetyl*-*β*-*D*-*arabinofuranosyl*)*sulfone*-6-[4-(*chlorophenyl*)-*methylene*]-*amino*-2-(*methylsulfone*)-*pyrimidin*-4(1*H*)-*one* (7*a*).** It was obtained from 6 and 1-bromo-2,3,5-tri-O-acetyl-*α*-D-arabinofuranose; as yellow powder, m. p. 253˚C - 255˚C; IR (cm^{-1}, *v*); 1712 (3CO), 1678 (CO); ^{1}H.NMR: *δ* 1.98, 2.02, 2.11 (3s, $3CH_3CO$), 2.50 (s, SCH_3), 4.02 (m, H-4'), 4.14 (m, H-5', H-5''), 5.27 (m, H-3'), 5.33 (m, H-2'), 6.61 (d, J = 3.70 Hz, H-1'), 7.33 (d, J = 7.50 Hz, Ar-H), 7.88 (d, J = 7.50 Hz, Ar-H), 8.12 (s, pyrimidine-H), 8.38 (s, CH); ^{13}C. NMR: 20.39, 21.89, 22.74 ($3CH_3$), 30.17 (SCH_3), 61.31 (C-5'), 65.35 (C-3'), 66.79 (C-2'), 66.89 (C-4'), 86.56 (C-1'), 125.1 - 149.2 (10C-Ar), 167.3 (CO), 169.2, 170.4, 172.8 (3CO); Its MS (m/z), 569 (M^+, 61%); $C_{23}H_{24}ClN_3O_{10}S$ (569.9).

***N*-(2',3',5'-*tri*-*O*-*benzoyl*-*β*-*D*-*ribofuranosyl*)*sulfone*-6-[4-(*chlorophenyl*)-*methylene*]-*amino*-2-(*methylsulfone*)*pyrimidin*-4(1*H*)-*one* (7*b*).** It was obtained from 6 and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as yellow powder, m. p. 304˚C - 306˚C; IR (cm^{-1}, *v*); 1728 (3CO), 1672 (CO), 1335 (SO); ^{1}H.NMR: *δ* 2.23 (s, CH_3), 3.89 (m, H-4'), 4.09 (m, H-5', H-5''), 5.19 (m, H-3'), 5.40 (m, H-2'), 6.78 (d, J = 3.65 Hz, H-1'), 7.13 - 8.03 (m, 19H, Ar-H), 8.42 (s, pyrimidine-H), 8.76 (s, CH); Its MS (m/z), 756 (M^+, 54%); $C_{38}H_{30}N_3O_{10}S$ (756.1).

Synthesis of diacetylated 2-{S-(*β*-*D*-glycofuranosyl)-6-[4-(chlorophenyl)methylene]-aminopyrimidin-4(1*H*)-one (5a,b) and (8a,b); *General procedure*: Acetylated compound 4a,b or 7a,b (1.0 mmol) was dissolved in methanolic ammonia (saturated with NH_3 at 0˚C, 100 ml). The reaction mixture was stirred overnight and then heated the reaction mixture for 1 h at 120˚C - 130˚C. The mixture was then cooled and the solvent was evaporated to provide the crude nucleoside. The crude was purified by heating the crude in n-hexane (100 ml, three times) and crystallized from methanol (20 - 30 mL).

***N*-(*β*-*D*-*arabinofuranosyl*)-6-[4-(*chlorophenyl*)-*methylene*]*aminopyrimidin*-4(*1H*)-*one* (5*a*).** It was obtained from 4a, as white powder, m. p. 239˚C - 241˚C; IR (cm^{-1}, *v*); 3500 (brs, OH), 1676 (CO), 1330 (SO); ^{1}H.NMR: *δ* 2.34 (s, SCH_3), 3.86 (m, *H*-5', *H*-5''), 4.09 (m, *H*-4'), 4.76 (t, *H*-2'), 5.08 (t, *J* = 5.41 Hz, *J* = 4.89 Hz, OH-C(5'), 5.24 (d, *J* = 4.48 Hz, OH-C(3'), 5.50 (d, *J* = 5.73 Hz, OH-C(2'), 5.72 (t, *J* = 9.76 Hz, *H*-3'), 6.91 (d, *J* = 5.66 Hz, *H*-1'), 7.28 (d, 2H, Ar-*H*), 8.07 (d, 2H, Ar-*H*), 8.35 (s, pyrimidine-*H*), 8.58 (s, C*H*); ^{13}C.NMR: 26.03 (SCH_3), 60.91 (*C*-5'), 65.29 (*C*-3'), 67.45 (*C*-2'), 69.19 (*C*-4'), 87.67 (*C*-1'), 121.6 - 147.7 (10*C*-*Ar*), 167.5 (*C*O); Its MS (m/z), 411 (M^+, 31%); $C_{17}H_{18}ClN_3O_5S$ (411.8).

***N*-(*β*-*D*-*ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*aminopyrimidin*-4(1*H*)-*one* (5*b*).** It was obtained from 4b, as white powder, m. p. 221˚C - 223˚C; IR (cm^{-1}, *v*); 3486 (brs, OH), 1682 (CO); ^{1}H.NMR: *δ* 2.38 (s, SCH_3), 3.84 (m, *H*-5', *H*-5''), 4.04 (m, *H*-4'), 4.75 (t, *H*-2'), 5.06 (t, *J* = 5.40 Hz, *J* = 4.86 Hz, OH-C(5'), 5.26 (d, *J* = 4.47 Hz, OH-C(3'), 5.52 (d, *J* = 5.71 Hz, OH-C(2'), 5.72 (t, *J* = 9.74 Hz, *H*-3'), 6.90 (d, *J* = 5.67 Hz, *H*-1'), 7.30 (d, 2H, Ar-*H*), 8.08 (d, 2H, Ar-*H*), 8.38 (s, pyrimidine-*H*), 8.64 (s, C*H*); ^{13}C.NMR: 26.35 (SCH_3), 60.78 (*C*-5'), 65.31 (*C*-3'), 67.54 (*C*-2'), 70.11 (*C*-4'), 88.23 (*C*-1'), 121.9 - 148.5 (10*C*-*Ar*), 167.8 (*C*O); Its MS (m/z), 411 (M^+, 27%); $C_{17}H_{18}ClN_3O_5S$ (411.8).

***N*-(*β*-*D*-*arabinofuranosyl*)*sulfone*-6-[4-(*chlorophenyl*)*methylene*]*aminopyrimidin*-4(1*H*)-*one* (8*a*).** It was obtained from 7a, as white powder, m. p. 271˚C - 273˚C; IR (cm^{-1}, *v*); 3470 (brs, OH), 1680 (CO), 1320 (SO); ^{1}H.NMR: *δ* 2.45 (s, SCH_3), 3.90 (m, *H*-5', *H*-5''), 4.05 (m, *H*-4'), 4.82 (t, *H*-2'), 5.11 (t, *J* = 5.36 Hz, *J* = 4.91 Hz, OH-C(5'), 5.21 (d, *J* = 4.50 Hz, OH-C(3'), 5.46 (d, *J* = 5.67 Hz, OH-C(2'), 5.68 (t, *J* = 9.73 Hz, *H*-3'), 6.79 (d, *J* = 5.66 Hz, *H*-1'), 7.23 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.20 (s, pyrimidine-*H*), 8.65 (s, C*H*); ^{13}C.NMR: 27.01 (SCH_3), 61.21 (*C*-5'), 65.32 (*C*-3'), 67.54 (*C*-2'), 69.22 (*C*-4'), 86.97 (*C*-1'), 122.3 - 147.9 (10*C*-*Ar*), 166.8 (*C*O); Its MS (m/z), 443 (M^+, 34%); $C_{17}H_{18}ClN_3O_7S$ (443.8).

***N*-(*β*-*D*-*ribofuranosyl*)*sulfone*-6-[4-(*chlorophenyl*)*methylene*]*aminopyrimidin*-4(1*H*)-*one* (8*b*).** It was obtained from 7b, as white powder, m. p. 263˚C - 265˚C; IR (cm^{-1}, *v*); 3485 (brs, OH), 1680 (CO), 1315 (SO); ^{1}H.NMR: *δ* 2.42 (s, SCH_3), 3.73 (m, *H*-5', *H*-5''), 4.08 (m, *H*-4'), 4.82 (t, *H*-2'), 5.15 (t, *J* = 5.38 Hz, *J* = 4.87 Hz, OH-C(5'), 5.23 (d, *J* = 5.46 Hz, OH-C(3'), 5.48 (d, *J* = 3.67 Hz, OH-C(2'), 5.70 (t, *J* = 9.69 Hz, *H*-3'), 6.81 (d, *J* = 3.59 Hz, *H*-1'), 7.25 (d, Ar-*H*), 8.06 (d, Ar-*H*), 8.42 (s, pyrimidine-*H*), 8.68 (s, C*H*); ^{13}C.NMR: 27.16 (SCH_3), 61.32 (*C*-5'), 65.41 (*C*-3'), 67.69 (*C*-2'), 69.34 (*C*-4'), 86.94 (*C*-1'), 122.6-149.0 (10*C*-*Ar*), 167.4 (*C*O); Its MS (m/z), 443 (M^+, 41%); $C_{17}H_{18}ClN_3O_7S$ (443.8).

Synthesis of 2-alkylamino-6-[4-(chlorophenyl)methylene]aminopyrimidin-4(1*H*)-one (9a-c). General procedure: A mixture of 3 (10 m mol) fused with morphline/methylpiprazine/and or piprazine (15 m mol) in sand bath at 180˚C for 3 h. The reaction mixture was allowed to cool to room temp., and then add ethanol (20 mL), the precipitate was filtered off, dried and crystallized from an appropriate solvent to produce 9a-c.

***Synthesis of* 6-[4-(*chlorophenyl*)*methylene*]*amino*-2-*morpholin*-4-*ylpyrimidin*-4(3*H*)-*one* (9*a*).** It was obtained from morpholine (15 m mol) as a apale yellow powder crystallized from dioxane in 68% yield; m. p. 254˚C - 256˚C, IR (cm^{-1}, *ν*): 1678 (CO); ^{1}H NMR: *δ* 3.23 (t, $2NCH_2$, *J* = 4.87 Hz), 3.56 (t, $2OCH_2$, *J* = 4.95 Hz), 7.31

(d, *J* = 7.46 Hz, Ar-*H*), 7.86 (d, *J* = 7.48 Hz, Ar-*H*), 8.07 (s, pyrimidine-*H*), 8.58 (s, C*H*); C^{13} NMR: 167.4 (CO), 122.6 - 156.8 (10C Ar), 66.54, 47.09 (4C, O(CH_2)$_2$, N(CH_2)$_2$); Its MS (m/z), 318 (M^+, 69%); $C_{15}H_{15}ClN_4O_2$ (318.7).

***Synthesis of* 6-[4-(*chlorophenyl*)*methylene*]*amino*-2-*piprazin*-1-*ylpyrimidin*-4(3*H*)-*one* (9*b*).** It was obtained from piprazine (15 m mol) as a yellow powder crystallized from DMF in 72% yield; m. p. 232˚C - 234˚C, IR (cm^{-1}, *ν*): 3390 (br, NH), 1669 (CO); 1H NMR: *δ* 2.54 (br, 2NCH2), 3.37 (br, 2NCH$_2$), 7.26 (d, J = 7.48 Hz, Ar-H), 7.89 (d, J = 7.50 Hz, Ar-H), 8.12 (s, pyrimidine-H), 8.67 (s, CH); 9.34 (br, NH); C13 NMR: 164.9 (CO), 161.4 (C-2, pyrimidine), 123.2 - 157.1 (10C Ar)), 56.47, 46.18 (4C, N(CH_2)$_2$, N(CH_2)$_2$); Its MS (m/z), 317 (M^+, 29%); $C_{15}H_{16}ClN_5O$ (317.7).

***Synthesis of* 6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*methylpiprazine*-1-*yl*) *pyrimidin*-4(3*H*)-*one* (9*c*).** It was obtained from methylpiprazine (15 m mol) as a pale yellow powder crystallized from DMF in 65% yield; m. p. 273˚C - 275˚C, IR (cm^{-1}, *ν*): 1667 (CO); ^{1}H NMR: *δ* 2.32 (s, NCH_3), 2.50 (br, 2NCH_2), 3.29 (br, 2NCH_2), 7.28 (d, *J* = 7.50 Hz, Ar-*H*), 7.92 (d, *J* = 7.50 Hz, Ar-*H*), 8.17 (s, pyrimidine-*H*), 8.73 (s, C*H*); Its MS (m/z), 331 (M^+, 38%); $C_{16}H_{18}ClN_5O$ (331.3).

Preparation of the acetylated N-nucleosides of 6-[4-(chlorophenyl)methylene]amino-2-(4-alkylamino)-pyrimidin-4(3*H*)-one (10a-f); *General procedure*: To a solution of each of 9a-c (0.01 mol) in aqueous potassium hydroxide (0.01 mol) in distilled water (5 ml) was added a solution of 1-bromo-2,3,5-tri-*O*-acetyl-*α*-*D*-arabino-furanose/2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide (0.015 mol) in acetone (40 ml). The reaction mixture was stirred at room temperature for 24 h (under TLC control). The solvent was evaporated under reduced pressure at 40˚C, and the crude product was washed with distilled water to remove KBr formed, the product was collected, dried, and crystallized from ethanol (50 - 80 mL).

***N*-(2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*morpholin*-4-*yl*) *pyrimidin*-4(3*H*)-*one* (10*a*).** It was obtained from 9a and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as white powder, m. p. 187˚C - 189˚C; IR (cm^{-1}, *ν*); 1734 (3CO), 1683 (CO); ^{1}H.NMR: *δ* 1.93, 1.99, 2.11 (3s, 3CH_3CO), 2.54 (m, N(CH_2)$_2$), 3.61 (m, O(CH_2)$_2$), 4.13 (m, H-4'), 4.18 (m, H-5', H-5''), 5.31 (m, H-3'), 5.39 (m, H-2'), 6.81 (d, J = 3.72 Hz, H-1'), 7.23 (d, Ar-H), 7.79 (d, Ar-H), 8.15 (s, pyrimidine-H), 8.83 (s, CH); ^{13}C.NMR: 22.20, 22.31, 22.57 (3CH_3), 45.76 (2C, N(CH_2)$_2$), 60.98 (C-5'), 63.28 (2C, O(CH_2)$_2$), 66.30 (C-3'), 66.87 (C-2'), 67.41 (C-4'), 86.03 (C-1'), 124.8-148.3 (10C-Ar), 166.8 (CO), 170.1, 171.3, 172.5 (3CO); Its MS (m/z), 576 (M^+, 21%); $C_{26}H_{29}ClN_4O_9$ (576.9).

***N*-(2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*morpholin*-4-*yl*) *pyrimidin*-4(3*H*)-*one* (10*b*).** It was obtained from 9a and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide as pale yellow powder, m. p. 289˚C - 291˚C; IR (cm^{-1}, *ν*); 1737 (3CO), 1680 (CO); ^{1}H.NMR: *δ* 2.53 (m, N(CH_2)$_2$), 3.51 (m, O(CH_2)$_2$), 4.07 (m, H-4'), 4.19 (m, H-5', H-5''), 5.23 (m, H-3'), 5.37 (m, H-2'), 6.72 (d, J = 3.65 Hz, H-1'), 7.12 - 8.08 (m, 19H, Ar-H), 8.35 (s, pyrimidine-H), 8.74 (s, CH); ^{13}C. NMR: 43.56 (2C, HN(CH_2)$_2$), 45.11 (2C, N(CH_2)$_2$), 61.39 (C-5'), 65.04 (2C, O(CH_2)$_2$), 66.14 (C-3'), 67.82 (C-2'), 69.30 (C-4'), 85.31 (C-1'), 123.1 - 157.6 (28C-Ar), 166.5 (CO), 170.5, 172.3, 173.8 (3CO); Its MS (m/z), 763 (M^+, 19%); $C_{41}H_{35}ClN_4O_9$ (763.1).

***N*-(2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*piprazin*-1-*yl*) *pyrimidin*-4(3*H*)-*one* (10*c*).** It was obtained from 9b and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as white powder, m. p. 212˚C - 214˚C; IR (cm^{-1}, *ν*); 3355 (NH), 1728 (3CO), 1672 (CO); ^{1}H.NMR: *δ* 1.98, 2.00, 2.09 (3s, 3CH_3CO), 2.45 (m, N(CH_2)$_2$), 3.03 (m, HN(CH_2)$_2$), 4.08 (m, H-4'), 4.15 (m, H-5', H-5''), 5.31 (m, H-3'), 5.38 (m, H-2'), 6.73 (d, J = 3.67 Hz, H-1'), 7.24 (d, Ar-H), 7.81 (d, Ar-H), 8.25 (s, pyrimidine-H), 8.82 (s, CH), 10.12 (br, NH D_2O exchangeable); ^{13}C. NMR: 22.17, 22.25, 22.63 (3CH_3), 43.74 (2C, HN(CH_2)$_2$), 45.87 (2C, N(CH_2)$_2$), 61.55 (C-5'), 66.31 (C-3'), 66.81 (C-2'), 67.35 (C-4'), 85.73 (C-1'), 124.3 - 156.5 (10C-Ar), 166.8 (CO), 169.4, 170.6, 172.9 (3CO); Its MS (m/z), 575 (M^+, 28%); $C_{26}H_{30}ClN_5O_8$ (575.9).

***N*-(2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*piprazin*-1-*yl*) *pyrimidin*-4(3*H*)-*one* (10*d*).** It was obtained from 9b and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as yellow powder, m. p. 261˚C - 263˚C; IR (cm^{-1}, *ν*); 1721 (3CO), 1681 (CO); ^{1}H.NMR: *δ* 2.34 (m, N(CH_2)$_2$), 3.21 (m, N(CH_2)$_2$), 4.08 (m, H-4'), 4.19 (m, H-5', H-5''), 5.28 (m, H-3'), 5.37 (m, H-2'), 6.78 (d, J = 3.63 Hz, H-1'), 7.11 - 8.02 (m, 19H, Ar-H), 8.40 (s, pyrimidine-H), 8.69 (s, CH); Its MS (m/z), 762 (M^+, 37%); $C_{41}H_{36}ClN_5O_8$ (762.2).

***N*-(2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*methylpiprazin*-1-*yl*)*pyrimidin*-4(3*H*)-*one* (10*e*).** It was obtained from 9c and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as yellow powder, m. p. 209˚C - 211˚C; IR (cm^{-1}, *ν*); 1728 (3CO), 1672 (CO); ^{1}H.NMR: *δ* 1.93, 1.99, 2.11 (3s, 3CH_3CO), 2.32 (s, CH_3), 2.45 (m, N(CH_2)$_2$), 3.03 (m, HN(CH_2)$_2$), 4.13 (m, H-4'), 4.18 (m, H-5', H-5''), 5.31 (m, H-3'), 5.39 (m, H-2'), 6.81 (d, J = 3.72 Hz, H-1'), 7.27 (d, Ar-H), 8.00 (d, Ar-H), 8.43 (s, pyrimidine-H), 8.89 (s, CH); ^{13}C.NMR: 22.21, 22.30, 22.57 (3CH_3), 30.05 (NCH_3), 43.76 (2C, N(CH_2)$_2$), 45.93 (2C, N(CH_2)$_2$), 60.98 (C-5'), 66.30 (C-3'), 66.87 (C-2'), 67.41 (C-4'), 86.03 (C-1'), 119.8-148.3 (10C-Ar), 166.8 (CO),

170.1, 171.3, 172.9 (3CO); Its MS (m/z), 590 (M^+, 21%); $C_{27}H_{32}ClN_5O_8S$ (590.9).

***N*-(2',3',5'-*tri*-*O*-benzoyl-*β*-*D*-ribofuranosyl)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*methylpiprazin*-1-*yl*)*pyrimidin*-4(3*H*)-*one* (10*f*).** It was obtained from 9c and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide as yellow powder, m. p. 281˚C - 283˚C; IR (cm^{-1}, *v*); 1719 (3CO), 1668 (CO); 2.28 (s, NCH_3), 2.49 (m, $N(CH_2)_2$), 3.26 (m, $N(CH_2)_2$), 4.06 (m, H-4'), 4.13 (m, H-5', H-5''), 5.30 (m, H-3'), 5.33 (m, H-2'), 6.73 (d, J = 3.66 Hz, H-1'), 7.16-8.11 (m, 19H, Ar-H), 8.35 (s, pyrimidine-H), 8.74 (s, CH); ^{13}C. NMR: 31.10 (NCH_3), 43.56 (2C, $HN(CH_2)_2$), 45.11 (2C, $N(CH_2)_2$), 60.69 (C-5'), 66.21 (C-3'), 66.76 (C-2'), 67.42 (C-4'), 85.58 (C-1'), 123.1 - 157.3 (28C-Ar), 165.9 (CO), 170.3, 171.3, 173.8 (3CO); Its MS (m/z), 776 (M^+, 19%); $C_{42}H_{38}ClN_5O_8$ (776.2).

Synthesis of diacetylated N-(-β-D-glycofuranosyl)-6-[4-(chlorophenyl)methylene]-amino-2-(4-alkylamino) pyrimidin-4(3H)-one (11a-f); (see 3.1.4, General procedures), and crystallized from ethanol (80 mL).

***N*-(*β*-*D*-*arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*] *amino*-2-(4-*morpholin*-4-*yl*)-*pyrimidin*-4(3*H*)-*one* (11*a*).** It was obtained from 10a; as yellow powder, m. p. 239˚C - 241˚C; IR (cm^{-1}, *v*);3450 (br, OH), 1686 (CO); ^{1}H.NMR: δ 2.39 (m, $N(CH_2)_2$), 3.56 (m, $O(CH_2)_2$), 3.88 (m, *H*-5', *H*-5''), 4.02 (m, *H*-4'), 4.78 (t, *H*-2'), 5.09 (t, *J* = 5.33 Hz, *J* = 4.87 Hz, OH-C(5'), 5.19 (d, *J* = 4.47 Hz, OH-C(3'), 5.39 (d, *J* = 5.63 Hz, OH-C(2'), 5.70 (t, *J* = 9.67 Hz, *H*-3'), 6.81 (d, *J* = 5.68 Hz, *H*-1'), 7.30 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.36 (s, pyrimidine-*H*), 8.92 (s, C*H*); ^{13}C. NMR: 43.71 (2C, $HN(CH_2)_2$), 61.52 (*C*-5'), 63.28 (2C, $O(CH_2)_2$), 66.23 (*C*-3'), 66.78 (*C*-2'), 67.37 (*C*-4'), 85.73 (*C*-1'), 124.6 - 155.8 (10*C*-*Ar*), 167.8 (*C*O); Its MS (m/z), 450 (M^+, 28%); $C_{20}H_{23}ClN_4O_6$ (450.8).

***N*-(*β*-*D*-*ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*] *amino*-2-(4-*morpholin*-4-*yl*)*pyri*-*midin*-4(3*H*)-*one* (11*b*).** It was obtained from 10b; as a yellow powder, m. p. 223˚C - 225˚C; IR (cm^{-1}, *v*); 3435 (OH), 1676 (CO); ^{1}H.NMR: δ 2.32 (m, $N(CH_2)_2$), 3.52 (m, $O(CH_2)_2$), 3.90 (m, *H*-5', *H*-5''), 4.05 (m, *H*-4'), 4.81 (t, *H*-2'), 5.12 (t, *J* = 5.35 Hz, *J* = 4.88 Hz, OH-C(5'), 5.23 (d, *J* = 4.52 Hz, OH-C(3'), 5.42 (d, *J* = 5.70 Hz, OH-C(2'), 5.70 (t, *J* = 9.72 Hz, *H*-3'), 6.86 (d, *J* = 5.70 Hz, *H*-1'), 7.28 (d, Ar-*H*), 7.97 (d, Ar-*H*), 8.32 (s, pyrimidine-*H*), 8.86 (s, C*H*; Its MS (m/z), 450 (M^+, 32%); $C_{20}H_{23}ClN_4O_6$ (450.8).

***N*-(*β*-*D*-*arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*piprazin*-1-*yl*)-*pyrimidin*-4(3*H*)-*one* (11*c*).** It was obtained from 10c; as yellow powder, m. p. 268˚C - 270˚C; IR (cm^{-1}, *v*); 3425 (brs, OH), 3328 (br, NH) 1672 (CO); ^{1}H.NMR: δ 2.48 (m, $N(CH_2)_2$), 3.19 (m, $O(CH_2)_2$), 3.81 (m, *H*-5', *H*-5''), 3.98 (m, *H*-4'), 4.69 (t, *H*-2'), 5.09 (t, *J* = 5.41 Hz, *J* = 4.88 Hz, OH-C(5'), 5.26 (d, *J* = 4.47 Hz, OH-C(3'), 5.47 (d, *J* = 5.61 Hz, OH-C(2'), 5.70 (t, *J* = 9.78 Hz, *H*-3'), 6.79 (d, *J* = 5.60 Hz, *H*-1'), 7.30 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.41 (s, pyrimidine-*H*), 8.67 (s, C*H*), 9.46 (brs, N*H*); ^{13}C.NMR: 42.83 (2C, $HN(CH_2)_2$), 46.39 (2C, $HN(CH_2)_2$), 60.88 (*C*-5'), 64.81 (*C*-3'), 67.23 (*C*-2'), 70.16 (*C*-4'), 87.09 (*C*-1'), 125.8 - 156.6 (10*C*-*Ar*), 165.9 (*C*O); Its MS (m/z), 449 (M^+, 36%); $C_{20}H_{24}ClN_5O_5$ (449.8).

***N*-(*β*-*D*-*ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*] *amino*-2-(4-*piprazin*-1-*yl*)*pyrim*-*idin*-4(3*H*)-*one* (11*d*).** It was obtained from 10d; as yellow powder, m. p. 252˚C - 254˚C; IR (cm^{-1}, *v*); 3480 (brs, OH), 3290 (br, NH), 1668 (CO); ^{1}H.NMR: δ 2.53 (m, $N(CH_2)_2$), 3.21 (m, $O(CH_2)_2$), 3.89 (m, *H*-5', *H*-5''), 4.03 (m, *H*-4'), 4.73 (t, *H*-2'), 5.12 (t, *J* = 5.49 Hz, *J* = 4.90 Hz, OH-C(5'), 5.29 (d, *J* = 4.51 Hz, OH-C(3'), 5.51 (d, *J* = 5.59 Hz, OH-C(2'), 5.83 (t, *J* = 9.80 Hz, *H*-3'), 6.81 (d, *J* = 5.56 Hz, *H*-1'), 7.29 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.38 (s, pyrimidine-*H*), 8.80 (s, C*H*), 9.60 (brs, N*H*); Its MS (m/z), 449 (M^+, 29%); $C_{20}H_{24}ClN_5O_5$ (449.8).

***N*-(*β*-*D*-*arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]*amino*-2-(4-*methylpiprazin*-1-*yl*)*pyrimidin*-4(3*H*)-*one* (11*e*).** It was obtained from 10e; as yellow powder, m. p. 239˚C - 241˚C; IR (cm^{-1}, *v*); 3456 (brs, OH), 1683 (CO); ^{1}H.NMR: δ 2.29 (s, CH_3), 2.53 (m, $N(CH_2)_2$), 3.07 (m, $HN(CH_2)_2$), 3.91 (m, *H*-5', *H*-5''), 4.05 (m, *H*-4'), 4.80 (t, *H*-2'), 5.13 (t, *J* = 5.40 Hz, *J* = 4.85 Hz, OH-C(5'), 5.25 (d, *J* = 4.48 Hz, OH-C(3'), 5.50 (d, *J* = 5.65 Hz, OH-C(2'), 5.73 (t, *J* = 9.72 Hz, *H*-3'), 6.83 (d, *J* = 5.61 Hz, *H*-1'), 7.21 (d, Ar-*H*), 7.96 (d, Ar-*H*), 8.35 (s, pyrimidine-*H*), 8.70 (s, C*H*); ^{13}C.NMR: 30.16 (NCH_3), 43.51 (2C, $N(CH_2)_2$), 45.87 (2C, $N(CH_2)_2$), 61.08 (*C*-5'), 66.51 (*C*-3'), 66.90 (*C*-2'), 67.47 (*C*-4'), 86.12 (*C*-1'), 126.7 - 154.9 (10*C*-*Ar*), 166.4 (*C*O); Its MS (m/z), 463 (M^+, 27%); $C_{21}H_{26}ClN_5O_5$ (463.9).

***N*-(*β*-*D*-*ribofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*] *amino*-2-(4-*methylpiprazin*-1-*yl*)*pyrimidin*-4(3*H*)-*one* (11*f*).** It was obtained from 10f as yellow powder, m. p. 247˚C - 249˚C; IR (cm^{-1}, *v*); 3428 (brs, OH), 1689 (CO); ^{1}H.NMR: δ 2.26 (s, CH_3), 2.52 (m, $N(CH_2)_2$), 3.05 (m, $HN(CH_2)_2$), 3.40 (m, *H*-5', *H*-5''), 4.12 (m, *H*-4'), 4.85 (t, *H*-2'), 5.18 (t, *J* = 5.47 Hz, *J* = 4.90 Hz, OH-C(5'), 5.31 (d, *J* = 4.51 Hz, OH-C(3'), 5.62 (d, *J* = 5.67 Hz, OH-C(2'), 5.76 (t, *J* = 9.77 Hz, *H*-3'), 6.81 (d, *J* = 5.64 Hz, *H*-1'), 7.24 (d, Ar-*H*), 7.99 (d, Ar-*H*), 8.39 (s, pyrimidine-*H*), 8.81 (s, C*H*); Its MS (m/z), 463 (M^+, 31%); $C_{21}H_{26}ClN_5O_5$ (463.9).

Synthesis of 4-[(4-aryl)methylene]amino-6-chloro-pyrimidine-2-thiol (13). A solution of 2a (0.01 mol) in dry dioxane (40 mL) was treated with 10 mL of phosphorus oxychloride, and the mixture was stirred under reflux for 5 h. The reaction mixture was allowed to cool to 25˚C, and poured into cold water (100 mL), a solid was separated, filtered off, and crystallized from the benzene (50 mL), as yellow powder, m. p. 178˚C - 179˚C ; IR (cm^{-1}, *v*); 3245 (br, NH); 1H.NMR: δ 7.20 (d,

J = 7.50 Hz, Ar-H), 7.99 (d, *J* = 7.50 Hz, Ar-H), 8.39 (s, pyrimidine-H), 8.81 (s, CH); Its MS (m/z), 284 (M+, 31%), 285 (M^+ +1, 21%); C11H7Cl2N3S (284.1).

Synthesis of 4-[(4-chlorophenyl)methylene]amino-6-(4-alkylamino-yl)pyrimidine-2-thiol (14a-c). General procedure: A mixture of each of compound 13 (10 m mol) fused with morphline/methylpiprazine/ and or piprazine (15 m mol) in sand bath at 180˚C for 2 h. The reaction mixture was allowed to cool to room temp., and then add ethanol (20 mL), the precipitate was filtered off, dried and crystallized from dimethyl formamide to produce 14a-c.

4-[(4-*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyrimidine*-2-*thiol* (14*a*). It was obtained from morpholine (15 mmol) as a brown powder crystallized from dioxane in 71% yield; m. p. 286˚C - 288˚C, IR (cm^{-1}, *ν*): 3410 (br, NH); 1H NMR: *δ* 3.26 (t, $2NCH_2$, *J* = 4.87 Hz), 3.51 (t, 2OCH2, *J* = 4.95 Hz), 7.25 (d, *J* = 7.50 Hz, Ar-H), 7.96 (d, *J* = 7.48 Hz, Ar-H), 8.34 (s, pyrimidine-H), 8.63 (s, CH), 9.02 (br, NH); 13C NMR: 168.3 (C=S), 125.3 - 156.6 (10C Ar), 64.74 (4C, O(CH2)2), 47.09 (N(CH2)2); Its MS (m/z), 334 (M^+, 69%); $C_{15}H_{15}ClN_4OS$ (334.8).

4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*ylpyrimidine*-2-*thiol* (14*b*). It was obtained from piprazine (15 mmol) as a yellow powder crystallized from DMF in 68 % yield; m. p. 261˚C - 263˚C, IR (cm^{-1}, *ν*): 3390 (br, NH); ^{1}H NMR: *δ* 2.53 (brs, $2NCH_2$), 3.36 (brs, $2NCH_2$), 7.18 (d, *J* = 7.47 Hz, Ar-*H*),7.66 (d, *J* = 7.50 Hz, Ar-*H*), 8.29 (s, pyrimidine-*H*), 8.71 (s, C*H*), 9.16 (br, NH), 9.65 (br, N*H*); Its MS (m/z), 333 (M^+, 29%); $C_{15}H_{16}ClN_5S$ (333.8).

4-[4-(*chlorophenyl*)*methylene*]*amino*-6-(4-*methylpiprazine*-1-*yl*)*pyrimi-dine*-2-*thiol* (14*c*). It was obtained from 4-methylpiprazine (15 mmol) as a pale yellow powder crystallized from DMF in 71% yield; m. p. 281˚C - 283˚C, IR (cm^{-1}, *ν*): 3345 (br, NH); ^{1}H NMR: *δ* 2.24 (s, NCH_3), 2.48 (m, $2NCH_2$), 3.29 (m, $2NCH_2$), 7.21 (d, *J* = 7.47 Hz, Ar-*H*), 7.75 (d, *J* = 7.50 Hz, Ar-*H*), 8.33 (s, pyrimidine-*H*), 8.87 (s, C*H*), 9.20 (brs, NH); Its MS (m/z), 347 (M^+, 38%); $C_{16}H_{18}ClN_5S$ (347.8).

Preparation of the acetylated S-nucleosides of 4-[4-(chlorophenyl)methylene]amino-6-(4-alkylamino)-pyrimidinee (15a-f). (See 3.1.7; General procedure), crystallized from ethanol (40 - 80 mL).

2-(*S*-2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]-*amino*-6-*morpholin*-4-*ylpyrimidine* (15*a*). It was obtained from 14a and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as white powder, m. p. 268˚C - 270˚C; IR (cm^{-1}, *ν*); 1741 (3CO); ^{1}H.NMR: *δ* 1.93, 1.99, 2.02 (3s, $3CH_3CO$), 3.19 (m, $N(CH_2)_2$), 3.53 (m, $O(CH_2)_2$), 4.03 (m, H-4'), 4.18 (m, H-5', H-5''), 5.29 (m, H-3'), 5.40 (m, H-2'), 6.81 (d, J = 3.70 Hz, H-1'), 7.28 (d, Ar-H), 7.98 (d, Ar-H), 8.56 (s, pyrimidine-H), 8.95 (s, CH); ^{13}C. NMR: 22.19, 22.24, 22.61 ($3CH_3$), 43.71 (2C, $HN(CH_2)_2$), 61.52 (C-5'), 65.93 (2C, $O(CH_2)_2$), 66.23 (C-3'), 66.78 (C-2'), 67.37 (C-4'), 85.73 (C-1'), 121.3 - 147.5 (11C-Ar), 168.9, 170.8, 172.5 (3CO); Its MS (m/z), 593 (M^+, 37%); $C_{26}H_{29}ClN_4O_8S$ (593.0).

***2*-(*S*-2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyrimidine* (15*b*).** It was obtained from 14a and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as pale yellow powder, m. p. 278˚C - 280˚C; IR (cm^{-1}, *ν*); 1737 (3CO); ^{1}H.NMR: *δ* 2.39 (m, $N(CH_2)_2$), 3.38 (m, $O(CH_2)_2$), 4.11 (m, H-4'), 4.18 (m, H-5', H-5''), 5.30 (m, H-3'), 5.37 (m, H-2'), 6.83 (d, *J* = 3.67 Hz, H-1'),7.09 - 8.00 (m, 19H, Ar-H), 8.29(s, pyrimidine-H), 8.76(s, CH); ^{13}C.NMR: 43.56 (2C, N $(CH_2)_2$), 61.40 (C-5'), 65.11 (2C, $O(CH_2)_2$), 66.23(C-3'), 68.84 (C-2'), 70.19 (C-4'), 84.78 (C-1'), 121.1 - 155.6 (29C-Ar),(CO), 169.9, 170.7, 173.4 (3CO); Its MS (m/z), 779(M^+, 23%);$C_{41}H_{35}ClN_4O_8S$ (779.2).

2-(*S*-2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]-*amino*-6-*piprazin*-1-*ylpyrimidine* (15*c*). It was obtained from 14b and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as yellow powder, m. p. 259˚C - 261˚C; IR (cm^{-1}, *ν*); 1728 (3CO); ^{1}H.NMR: *δ* 1.96, 1.99, 2.08 (3s, $3CH_3CO$), 2.57 (m, $N(CH_2)_2$), 3.21 (m, $N(CH_2)_2$), 4.11 (m, H-4'), 4.17 (m, H-5', H-5''), 5.28 (m, H-3'), 5.37 (m, H-2'), 6.80 (d, J = 3.73 Hz, H-1'), 7.31 (d, Ar-H), 8.02 (d, Ar-H), 8.30 (s, pyrimidine-H), 8.78 (s, CH); ^{13}C.NMR: 22.21, 22.30, 22.57 ($3CH_3$), 44.71 (2C, $N(CH_2)_2$), 46.28 (2C, $N(CH_2)_2$), 60.87 (C-5'), 66.26 (C-3'), 66.90(C-2'), 67.36 (C-4'), 86.00 (C-1'), 126.8 - 148.3 (11C-Ar),170.1, 171.3, 172.9 (3CO);Its MS (m/z),592(M^+,21%); $C_{26}H_{30}ClN_5O_7S$ (592.0).

2-(*S*-2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*ylpyrimidine* (15*d*). It was obtained from 14b and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as yellow powder, m. p. 263˚C - 265˚C; IR (cm^{-1}, *ν*); 1728 (3CO); ^{1}H.NMR: *δ* 2.36 (m, $N(CH_2)_2$), 3.21 (m, $N(CH_2)_2$), 4.09 (m, H-4'), 4.15 (m, H-5', H-5''), 5.28 (m, H-3'), 5.35 (m, H-2'), 6.78 (d, J = 3.70 Hz, H-1'), 7.07-8.02 (m, 19H, Ar-H), 8.29 (s, pyrimidine-H), 8.76 (s, CH); Its MS (m/z), 778 (M^+, 31%); $C_{41}H_{36}ClN_5O_7S$ (778.2).

2-(*S*-2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]-*amino*-6-(4-*methylpiprazin*-1-*yl*)*pyrimidine* (15*e*). It was obtained from 14c and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as yellow powder, m. p. 255˚C - 257˚C; IR (cm^{-1}, *ν*); 1721 (3CO); ^{1}H.NMR: *δ* 1.93, 1.99, 2.11 (3s, $3CH_3CO$), 2.28 (s, NCH_3), 2.54 (m, $N(CH_2)_2$), 3.26 (m, 4H, $N(CH_2)_2$), 4.13 (m, H-4'), 4.18 (m, H-5', H-5''), 5.31 (m, H-3'), 5.39 (m, H-2'), 6.81 (d, J = 3.72 Hz, H-1'), 7.27 (d, 2H, Ar-H), 7.95 (d, Ar-H), 8.34 (s, pyrimidine-H), 8.69 (s, CH); ^{13}C.NMR: 22.21, 22.30, 22.57 ($3CH_3$), 30.12 (N-CH_3), 45.76 (2C, $N(CH_2)_2$), 46.28 (2C, $N(CH_2)_2$), 60.98 (C- 5'),

66.30 (C-3'), 66.87 (C-2'), 67.41 (C-4'), 86.03 (C-1'), 123.4 - 151.5 (11C-Ar), 170.1, 171.3, 172.9 (3CO); Its MS (m/z), 606 (M^+, 31%); $C_{27}H_{32}ClN_5O_7S$ (606.0).

***2*-(*S*-2',3',5'-*tri*-*O*-*benzoyl*-*β*-*D*-*ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-(4-*methylpiprazin*-1-*yl*)*pyrimidine* (15*f*).** It was obtained from 14c and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide as yellow powder, m. p. 291˚C - 293˚C; IR (cm^{-1}, *v*); 1728 (3CO); ^{1}H.NMR: δ 2.23 (s, CH_3), 2.45 (m, $N(CH_2)_2$), 3.46 (m, $N(CH_2)_2$), 4.11 (m, H-4'), 4.21 (m, H-5', H-5''), 5.27 (m, H-3'), 5.34 (m, H-2'), 6.89 (d, J = 3.62 Hz, H-1'), 7.12 - 8.08 (m, 19H, Ar-H), 8.35 (s, pyrimidine-H), 8.79 (s, CH); ^{13}C.NMR: 29.90 (NCH_3), 44.90 (2C, $N(CH_2)_2$), 47.43 (2C, $N(CH_2)_2$), 60.76 (C-5'), 66.23 (C-3'), 66.76 (C-2'), 68.34 (C-4'), 87.01 (C-1'), 122.5 - 154.3 (29C-Ar), 170.2, 172.1, 173.7 (3CO); Its MS (m/z), 792 (M^+, 27%); $C_{42}H_{38}ClN_5O_7S$ (792.2).

Synthesis of diacetylated *S*-(-*β*-*D*-*glycofuranosyl*)-6-[4-(chlorophenyl)methylene]-amino-2-(4-alkylamino) pyrimidine (16a-f); (see 3.1.4, General procedures), crystallized from dimethyl formamide (30 - 50 mL).

2-[*S*-(*β*-*D*-*arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyrimidine* (16*a*). It was obtained from 15a; as white powder, m. p. 289 ^{o}C - 291^{o}C; IR (cm^{-1}, *v*); 3463 (OH); ^{1}H.NMR: δ 2.37 (m, $N(CH_2)_2$), 3.51 (m, $O(CH_2)_2$), 3.89 (m, *H*-5', *H*-5''), 4.01 (m, *H*-4'), 4.77 (t, *H*-2'), 5.10 (t, *J* = 5.34 Hz, *J* = 4.86 Hz, OH- C(5'), 5.23 (d, *J* = 4.49 Hz, OH-C(3'), 5.41 (d, *J* = 5.60 Hz, OH-C(2'), 5.70 (t, *J* = 9.72 Hz, *H*-3'), 6.85(d, *J* = 5.64 Hz, *H*-1'), 7.25 (d, Ar-*H*), 8.01 (d, Ar-*H*), 8.33 (s, pyrimidine-*H*), 8.80 (s, C*H*); ^{13}C. NMR: 43.70 (2C, $N(CH_2)_2$), 61.51 (*C*-5'), 64.29 (2C, $O(CH_2)_2$), 66.28 (*C*-3'), 66.83 (*C*-2'), 67.40 (*C*-4'), 85.76 (*C*-1'), 124.6 - 155.5 (10*C*-*Ar*); Its MS (m/z), 466 (M^+, 32%); $C_{20}H_{23}ClN_4O_5S$ (466.9).

2-[*S*-(*β*-*D*-*ribofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyr*-*imidin*-4(3*H*)-*one* (16*b*). It was obtained from 15b; as pale powder, m. p. 305˚C - 307˚C; IR (cm^{-1}, *v*); 3412 (OH); ^{1}H.NMR: δ 2.30 (m, $N(CH_2)_2$), 3.51 (m, $O(CH_2)_2$), 3.95 (m, *H*-5', *H*-5''), 4.07 (m, *H*-4'), 4.83 (t, *H*-2'), 5.18 (t, *J* = 5.40 Hz, *J* = 4.82 Hz, OH-C(5'), 5.27 (d, *J* = 4.55 Hz, OH-C(3'), 5.45 (d, *J* = 5.65 Hz, OH-C(2'), 5.71 (t, *J* = 9.73 Hz, *H*-3'), 6.87 (d, *J* = 5.70 Hz, *H*-1'), 7.29 (d, Ar-*H*), 7.98 (d, Ar-*H*), 8.32 (s, pyrimidine-*H*), 8.81 (s, C*H*); Its MS (m/z), 466 (M^+, 38%); $C_{20}H_{23}ClN_4O_5S$ (466.9).

2-[*S*-(*β*-*D*-*arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*yl*-*pyrimidine* (16*c*). It was obtained from 15c; as white powder, m. p. 295˚C - 297˚C; IR (cm^{-1}, *v*); 3443 (OH), 3368 (NH); ^{1}H.NMR: δ2.43 (m, $N(CH_2)_2$), 3.23 (m, $N(CH_2)_2$), 3.90 (m, *H*-5', *H*-5''), 3.99 (m, *H*-4'), 4.70 (t, *H*-2'), 5.14 (t, *J* = 5.44 Hz, *J* = 4.89 Hz, OH-C(5'), 5.28 (d, *J* = 4.54 Hz, OH-C(3'), 5.53 (d, *J* = 5.60 Hz, OH-C(2'), 5.73 (t, *J* = 9.83 Hz, *H*-3'), 6.76 (d, *J* = 5.57 Hz, *H*-1'), 7.30 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.38 (s, pyrimidine-*H*), 8.75 (s, C*H*), 9.46 (brs, N*H*); ^{13}C. NMR: 43.50 (2C, $HN(CH_2)_2$), 46.23 (2C, $HN(CH_2)_2$), 60.68 (*C*-5'), 64.79 (*C*-3'), 67.32 (*C*-2'), 70.23 (*C*-4'), 87.13 (*C*-1'), 125.8 -156.6 (11*C*-*Ar*); Its MS (m/z), 465 (M^+, 36%); $C_{20}H_{24}ClN_5O_4S$ (465.9).

2-[*S*-(*β*-*D*-*ribofuranosyl*)]-4-[4-(*chlorophenyl*)*methyl ene*]*amino*-6-*piprazin*-1-*yl*-*pyri*-*midine* (16*d*). It was obtained from 15d; as yellow powder, m. p. 283˚C - 285˚C; IR (cm^{-1}, *v*); 3456 (OH), 3290 (NH); ^{1}H.NMR: δ 2.46 (m, $N(CH_2)_2$), 3.20 (m, $N(CH_2)_2$), 3.88 (m, *H*-5', *H*-5''), 4.05 (m, *H*-4'), 4.74 (t, *H*-2'), 5.15 (t, *J* = 5.46 Hz, *J* = 4.87 Hz, OH-C(5'), 5.32 (d, *J* = 4.50 Hz, OH-C(3'), 5.54 (d, *J* = 5.61 Hz, OH-C(2'), 5.87 (t, *J* = 9.83 Hz, *H*-3'), 6.86 (d, *J* = 5.60 Hz, *H*-1'), 7.23 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.29 (s,pyrimidine-*H*), 8.79(s, C*H*), 9.25 (br, N*H*); Its MS (m/z), 465 (M^+, 33%); $C_{20}H_{24}ClN_5O_4S$ (465.9).

2-[*S*-(*β*-*D*-*arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*met hylene*]*amino*-6-(4-*methylpip*-*razin*-*1*-*yl*)*pyrimidine* (16*e*). It was obtained from 15e; as yellow powder, m. p. 278˚C - 280˚C; IR (cm^{-1}, *v*); 3437 (OH); ^{1}H.NMR: δ 2.31 (s, NCH_3), 2.46 (m, $N(CH_2)_2$), 3.12 (m, $N(CH_2)_2$), 3.97 (m, *H*-5', *H*-5''), 4.09 (m, *H*-4'), 4.78 (t, *H*-2'), 5.15 (t, *J* = 5.43 Hz, *J* = 4.89 Hz, OH-C(5'), 5.28 (d, *J* = 4.50 Hz, OH-C(3'), 5.48 (d, *J* = 5.70 Hz, OH-C(2'), 5.81 (t, *J* = 9.72 Hz, *H*-3'), 6.89 (d, *J* = 5.64 Hz, *H*-1'), 7.27 (d, Ar-*H*), 7.98 (d, Ar-*H*), 8.32 (s, pyrimidine-*H*), 8.78 (s, C*H*); ^{13}C.NMR: 30.21 (NCH_3), 43.65 (2C, $N(CH_2)_2$), 45.67 (2C, $N(CH_2)_2$), 61.43 (*C*-5'), 66.49 (*C*-3'), 66.94 (*C*-2'), 67.51 (*C*-4'), 86.19 (*C*-1'), 125.7-154.9 (11*C*-*Ar*); Its MS (m/z), 479 (M^+, 27%); $C_{21}H_{26}ClN_5O_4S$ (479.9).

2-[*S*-(*β*-*D*-*ribofuranosyl*)]-4-[4-(*chlorophenyl*)*methyl ene*]*amino*-6-(4-*methylpiprazin*-1-*yl*)*pyrimidine* (16*f*). It was obtained from 15f as yellow powder, m. p. 321˚C - 323˚C; IR (cm^{-1}, *v*); 3450 (OH); ^{1}H.NMR: δ 2.36 (s, NCH_3), 2.48 (m, $N(CH_2)_2$), 3.09 (m, $N(CH_2)_2$), 3.65 (m, *H*-5', *H*-5''), 4.11 (m, *H*-4'), 4.82 (t, *H*-2'), 5.19 (t, *J* = 5.50 Hz, *J* = 4.92 Hz, OH-C(5'), 5.34 (d, *J* = 4.50 Hz, OH-C(3'), 5.66 (d, *J* = 5.69 Hz, OH-C(2'), 5.78 (t, *J* = 9.73 Hz, *H*-3'), 6.86 (d, *J* = 5.61 Hz, *H*-1'), 7.23 (d, *J* = 7.52 Hz, Ar-H), 7.98 (d, *J* = 7.51 Hz, Ar-H), 8.34 (s, pyrimidine-*H*), 8.74 (s, C*H*); Its MS (m/z), 479 (M^+, 27%); $C_{21}H_{26}ClN_5O_4S$ (479.9).

Preparation of the acetylated S-nucleoside sulfone of 4-[4-(chlorophenyl)-methylene]amino-6-(4-alkylamino) pyrimidinee (17a-f). *General procedure*: The solution of 15a-f (0.01 mol) in hydrogen peroxide solution (20 ml) (AcOH, H_2O_2; 2:1) was stirred at room temperature for 18 - 24 hs. (under TLC control). The solvent was evaporated under reduced pressure at 40˚C, and the crude product was filtered off. The product was dried, and crystallized from the ethanol (50 - 80 mL).

2-(*S*-2',3',5'-*tri*-*O*-*acetyl*-*β*-*D*-*arabinofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]-*amino*-6-*morpholin*-4-*ylpyri*

***midine* (17*a*).** It was obtained from 14a and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as white powder, m. p. 211˚C - 213˚C; IR (cm^{-1}, *v*); 1731 (3CO), 1320 (SO); ^{1}H.NMR: *δ* 1.98, 2.06, 2.14 (3s, $3CH_3CO$), 2.33 (s, CH_3), 2.49 (m, 4H, $N(CH_2)_2$), 3.35 (m, 4H, $O(CH_2)_2$), 4.11 (m, H-4'), 4.21 (m, H-5', H-5''), 5.35 (m, H-3'), 5.48 (m, H-2'), 6.81 (d, J = 3.69 Hz, H-1'), 7.31 (d, 2H, Ar-H), 8.03 (d, 2H, Ar-H), 8.32 (s, pyrimidine-H), 8.70 (s, CH) 10.25; ^{13}C. NMR: 22.19, 22.36, 22.89 ($3CH_3$), 43.72 (2C, $HN(CH_2)_2$), 61.53 (C-5'), 64.65 (2C, $O(CH_2)_2$), 66.19 (C-3'), 66.83 (C-2'), 67.40 (C-4'), 85.76 (C-1'), 123.3-153.5 (11C-Ar), 169.8, 170.6, 173.5 (3CO); Its MS (m/z), 625 (M^+, 42%); $C_{26}H_{29}ClN_4O_{10}S$ (625.0).

2-(*S*-2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyrimidine* (17*b*). It was obtained from 14a and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as yellow powde, m. p. 307˚C - 309˚C; IR (cm^{-1}, *v*); 1729 (3CO), 1336 (SO); ^{1}H.NMR: *δ* 2.50 (m, 4H, $N(CH_2)_2$), 3.36 (m, 4H, $O(CH_2)_2$), 4.08 (m, H-4'), 4.19 (m, H-5', H-5''), 5.31 (m, H-3'), 5.47 (m, H-2'), 6.77 (d, J = 3.70 Hz, H-1'), 7.12 - 8.00 (m, 19H, Ar-H), 8.32 (s, pyrimidine-H), 8.90 (s, CH); ^{13}C. NMR: 43.58 (2C, $HN(CH_2)_2$), 61.37 (C-5'), 65.12 (2C, $O(CH_2)_2$), 66.19 (C-3'), 66.84 (C-2'), 67.36 (C-4'), 85.66 (C-1'), 123.5-156.9 (29C-Ar), 169.7, 171.0, 174.1 (3CO); Its MS (m/z), 811 (M^+, 19%); $C_{41}H_{35}N_4O_{10}S$ (811.2).

2-(*S*-2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-6-[4-(*chlorophenyl*)*methylene*]-*amino*-6-*piprazin*-1-*ylpyrimidine* (17*c*). It was obtained from 14b and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as yellow powder, m. p. 234˚C - 236˚C; IR (cm^{-1}, *v*); 3240 (NH),1724 (3CO), 1330 (SO); ^{1}H.NMR: *δ* 1.95, 1.99, 2.14 (3s, $3CH_3CO$), 2.49 (m, $N(CH_2)_2$), 3.43 (m, $HN(CH_2)_2$), 4.15 (m, H-4'), 4.22 (m, H-5', H-5''), 5.33 (m, H-3'), 5.42 (m, H-2'), 6.84 (d, J = 3.69 Hz, H-1'), 7.28 (d, 2H, Ar-H), 7.98 (d, 2H, Ar-H), 8.40 (s, pyrimidine-H), 8.81 (s, CH), 9.18 (br, NH); Its MS (m/z), 624 (M^+, 33%); $C_{26}H_{30}ClN_5O_9S$ (624.0).

2-(*S*-2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*ylpyrimidine* (17*d*). It was obtained from 14b and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide; as yellow powder, m. p. 281˚C - 283˚C; IR (cm^{-1}, *v*); 3280 (NH), 1719 (3CO), 1335(SO); ^{1}H.NMR: *δ* 2.50 (m, $N(CH_2)_2$), 3.47 (m, $N(CH_2)_2$, 4.09 (m, H-4'), 4.17 (m, H-5', H-5''), 5.36 (m, H-3'), 5.45 (m, H-2'), 6.78 (d, *J* = 3.73 Hz, H-1'), 7.15 - 8.04 (m, 19H, Ar-H), 8.34 (s, pyrimidine-H), 8.76 (s, CH), 9.11 (br, NH); Its MS (m/z), 810(M^+, 27%); $C_{41}H_{36}ClN_5O_9S$ (810.2).

2-(*S*-2',3',5'-*tri-O-acetyl-β-D-arabinofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]-*amino*-6-(4-*methylpiprazin*-1-*yl*)*pyrimidine* (17*e*). It was obtained from 14c and 2,3,5-tri-O-acetyl-*α*-D-arabinofuranosyl)-bromide; as yellow powder, m. p. 229˚C - 231˚C; IR (cm^{-1}, *v*); 1728 (3CO), 1321 (SO); ^{1}H.NMR: *δ* 1.96, 2.03, 2.16 (3s, $3CH_3CO$), 2.37 (s, NCH_3), 2.55 (m, $N(CH_2)_2$), 3.39 (m, $N(CH_2)_2$), 4.16 (m, H-4'), 4.21 (m, H-5', H-5''), 5.32 (m, H-3'), 5.43 (m, H-2'), 6.83 (d, J = 3.72 Hz, H-1'), 7.31 (d, 2H, Ar-H), 8.00 (d, 2H, Ar-H), 8.38 (s, pyrimidine-H), 8.86 (s, CH); ^{13}C.NMR: 29.97 (NCH_3), 45.65 (2C, $N(CH_2)_2$), 46.79 (2C, $N(CH_2)_2$), 61.09 (C-5'), 66.56 (C-3'), 67.07 (C-2'), 68.13 (C-4'), 86.21 (C-1'), 122.3 - 153.5 (11C-Ar), 170.9, 171.7, 173.2 (3CO); Its MS (m/z), 638 (M^+, 21%); $C_{27}H_{32}ClN_5O_9S$ (638.0).

2-(*S*-2',3',5'-*tri-O-benzoyl-β-D-ribofuranosyl*)-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-(4-*methylpiprazin*-1-*yl*)*pyrimidine* (17*f*). It was obtained from 14c and 2,3,5-Tri-O-benzoyl-*β*-D-ribofuranosyl bromide as yellow powder, m. p. 301˚C - 303˚C; IR (cm^{-1}, *v*); 1730 (3CO), 1335 (SO); ^{1}H.NMR: *δ* 2.31 (s, NCH_3), 2.50 (m, $N(CH_2)_2$), 3.53 (m, $N(CH_2)_2$), 4.14 (m, H-4'), 4.19 (m, H-5', H-5''), 5.32 (m, H-3'), 5.41 (m, H-2'), 6.85 (d, J = 3.70 Hz, H-1'), 7.10 - 8.01 (m, 19H, Ar-H), 8.31 (s, pyrimidine-H), 8.70 (s, CH); ^{13}C.NMR: 30.20 (NCH_3), 43.29 (2C, $N(CH_2)_2$), 45.73 (2C, $N(CH_2)_2$), 61.08 (C-5'), 66.19 (C-3'), 66.90 (C-2'), 67.43 (C-4'), 86.01 (C-1'), 125.3 - 154.8 (29C-Ar), 170.6, 171.4, 173.2 (3CO); Its MS (m/z), 824 (M^+, 18%); $C_{42}H_{38}ClN_5O_9S$ (824.2).

Synthesis of diacetylated S-(-*β-D*-glycofuranosyl)-6-[4-(chlorophenyl)methylene]-amino-2-(4-alkylamino) pyrimidine (18a-f); (see 3.1.4, General procedures) and crystallized from ethanol (50 - 70 mL) .

2-[*S*-(*β-D-arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*morpholin*-4-*ylpyrimidine* (18*a*). It was obtained from 17a; as white powder, m. p. 241˚C - 243˚C; IR (cm^{-1}, *v*); 3458 (OH), 3286 (NH), 1686 (CO), 1330 (SO); ^{1}H.NMR: *δ* 2.32 (m, $NC\mathit{H}_2)_2$), 3.45 (m, $O(C\mathit{H}_2)_2$), 3.94 (m, *H*-5', *H*-5''), 4.03 (m, *H*-4'), 4.79 (t, *H*-2'), 5.13 (t, *J* = 5.34 Hz, *J* = 4.88 Hz, OH-C(5'), 5.29 (d, *J* = 4.52 H*z*, OH-C(3'), 5.47 (d, *J* = 5.63 Hz, OH-C(2'), 5.73 (t, *J* = 9.76 Hz, *H*-3'), 6.84 (d, *J* = 5.62 Hz, *H*-1'), 7.26 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.31 (s, pyrimidine-*H*), 8.76 (s, C*H*); ^{13}C. NMR: 43.72 (2C, $N(C\mathit{H}_2)_2$), 61.50 (*C*-5'), 64.19 (2C, $O(C\mathit{H}_2)_2$), 66.31 (*C*-3'), 66.83 (*C*-2'), 67.42 (*C*-4'), 85.78 (*C*-1'), 124.9 - 155.7 (11*C-Ar*); Its MS (m/z), 498 (M^+, 28%); $C_{20}H_{23}ClN_4O_7S$ (498.9).

2-[S-(*β*-D-ribofuranosyl)]-4-[4-(chlorophenyl)methylene]amino-6-morpholin-4-yl-pyrimidin-4(3H)-one (18b). It was obtained from 17b; as pale yellow powder, m. p. 276˚C - 278˚C; IR (cm^{-1}, *v*); 3465 (OH), 3270 (NH) 1341 (SO); ^{1}H.NMR: *δ* 2.35 (m, $NC\mathit{H}_2)_2$), 3.47 (m, $O(C\mathit{H}_2)_2$), 3.96 (m, *H*-5', *H*-5''), 4.05 (m, *H*-4'), 4.87 (t, *H*-2'), 5.18 (t, *J* = 5.40 Hz, *J* = 4.81 Hz, OH-C(5'), 5.29 (d, *J* = 4.56 Hz, OH-C(3'), 5.49 (d, *J* = 5.63 ***Hz***, OH-C(2'), 5.74 (t, *J* = 9.78 Hz, *H*-3'), 6.86 (d, *J* = 5.72 Hz, *H*-1'), 7.35 (d, Ar-*H*), 8.11 (d, Ar-*H*), 8.36 (s, pyrimidine-*H*), 8.80 (s, C*H*); Its MS (m/z), 498 (M^+, 19%);

$C_{20}H_{23}ClN_4O_7S$ (498.9).

2-[*S*-(*β*-*D*-*arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*yl*-*pyrimidine* (18*c*). It was obtained from 17c; as yellow powder, m. p. 251˚C - 253˚C; IR (cm^{-1}, *v*); 3428 (br, OH), 3278 (NH), 1335 (SO); ^{1}H.NMR: δ 2.39 (m, N(CH_2)$_2$), 3.28 (m, N(CH_2)$_2$), 3.90 (m, *H*-5', *H*-5''), 3.99 (m, *H*-4'), 4.67 (t, *H*-2'), 5.13 (t, *J* = 5.45 Hz, *J* = 4.88 Hz, OH-C(5'), 5.26 (d, *J* = 4.52 Hz, OH-C(3'), 5.59 (d, *J* = 5.58 Hz, OH-C(2'), 5.76 (t, *J* = 9.84 Hz, *H*-3'), 6.78 (d, *J* = 5.59 Hz, *H*-1'), 7.30 (d, Ar-*H*), 8.03 (d, Ar-*H*), 8.39 (s, pyrimidine-*H*), 8.79 (s, C*H*), 9.21 (br, N*H*); ^{13}C.NMR: 43.51 (2C, HN(*C*H$_2$)$_2$), 46.25 (2C, HN(*C*H$_2$)$_2$), 60.68 (*C*-5'), 64.77 (*C*-3'), 67.35 (*C*-2'), 70.26 (*C*-4'), 87.19 (*C*-1'), 125.3 - 156.9 (11*C*-*Ar*); Its MS (m/z), 497 (M^+, 30%); $C_{20}H_{24}ClN_5O_6S$ (497.9).

2-[*S*-(*β*-*D*-*ribofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-*piprazin*-1-*yl*-*pyrimidine* (18*d*). It was obtained from 17d; as yellow powder, m. p. 269˚C - 271˚C; IR (cm^{-1}, *v*); 3435 (OH), 3268 (NH), 1335 (SO); ^{1}H.NMR: δ 2.43 (m, N(CH_2)$_2$), 3.21 (m, N(CH_2)$_2$), 3.85 (m, *H*-5', *H*-5''), 4.03 (m, *H*-4'), 4.74 (t, *H*-2'), 5.16 (t, *J* = 5.48 Hz, *J* = 4.85 Hz, OH-C(5'), 5.30(d, *J* = 4.51 Hz, OH-C (3'), 5.56 (d, *J* = 5.60 Hz, OH-C(2'), 5.86 (t, *J* = 9.81 Hz, *H*-3'), 6.89 (d, *J* = 5.59 Hz, *H*-1'),7.26 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.33 (s, pyrimidine-*H*), 8.81 (s, C*H*), 9.22 (br, N*H*); Its MS(m/z), 497(M^+, 24%); $C_{20}H_{24}ClN_5O_6S$ (497.9).

2-[*S*-(*β*-*D*-*arabinofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-(4-*methylpipr*-*azin*-1-*yl*)*pyrimidine* (18*e*). It was obtained from 17e; as yellow powder, m. p. 247˚C - 249˚C; IR (cm^{-1}, *v*); 3420 (OH), 1335 (SO); ^{1}H.NMR: δ 2.35 (s, NCH_3), 2.49 (m, N(CH_2)$_2$), 3.17 (m, N(CH_2)$_2$), 3.96 (m, *H*-5', *H*-5''), 4.07 (m, *H*-4'), 4.78 (t, *H*-2'), 5.14 (t, *J* = 5.43 Hz, *J* = 4.91 Hz, OH-C(5'), 5.29 (d, *J* = 4.48 Hz, OH-C(3'), 5.51 (d, *J* = 5.67 Hz, OH-C(2'), 5.80 (t, *J* = 9.73 Hz, *H*-3'), 6.87 (d, *J* = 5.62 Hz, *H*-1'), 7.25 (d, Ar-*H*), 7.99 (d, Ar-*H*), 8.36 (s, pyrimidine-*H*), 8.74 (s, C*H*); ^{13}C.NMR: 30.20 (N*C*H$_3$), 43.68 (2C, N(*C*H$_2$)$_2$), 45.64 (2C, N(*C*H$_2$)$_2$), 61.49 (*C*-5'), 66.53 (*C*-3'), 66.96 (*C*-2'), 67.56 (*C*-4'), 86.21 (*C*-1'), 125.7 - 154.9 (11*C*-*Ar*); Its MS (m/z), 511 (M^+, 30%); $C_{21}H_{26}ClN_5O_6S$ (511.9).

2-[*S*-(*β*-*D*-*ribofuranosyl*)]-4-[4-(*chlorophenyl*)*methylene*]*amino*-6-(4-*methylpipra*-*zin*-1-*yl*)*pyrimidine* (18*f*). It was obtained from 17f as yellow powder, m. p. 287˚C - 289˚C; IR (cm^{-1}, *v*); 3400 (OH), 1335 (SO); ^{1}H.NMR: δ 2.33 (s, NCH_3), 2.45 (m, N(CH_2)$_2$), 3.19 (m, N(CH_2)$_2$), 3.89 (m, *H*-5', *H*-5''), 4.10 (m, *H*-4'), 4.82 (t, *H*-2'), 5.17 (t, *J* = 5.51 Hz, *J* = 4.93 Hz, OH-C(5'), 5.29 (d, *J* = 4.52 Hz, OH-C(3'), 5.63 (d, *J* = 5.71 Hz, OH-C(2'), 5.80 (t, *J* = 9.74 Hz, *H*-3'), 6.88 (d, *J* = 5.60 Hz, *H*-1'), 7.25 (d, *J* = 7.50 Hz, Ar-H), 8.01 (d, *J* = 7.51 Hz, Ar-H), 8.40 (s, pyrimidine-*H*), 8.75 (s, C*H*); Its MS (m/z), 511 (M^+, 28%); $C_{21}H_{26}ClN_5O_6S$ (511.9).

4.2. *In Vitro* Evaluation of Antiplatelet Aggregation Activity

The blood samples were obtained from healthy volunteers with negative history of smoking or taking any medications since 14d prior to blood collection. To blood samples was added trisodium citrate dihydrate 3.8% (1 part citrate, 9 part blood) and centrifuged at 1000 rpm for 8 min to obtain PRP. The remaining was centrifuged at 3000 rpm for 15 min and PPP was collected from the above layer which was used as the test blank. The platelet count was adjusted to 250,000 plts/mL by diluting PRP with appropriate amount of PPP once needed. Of the test compounds previously dissolved in dimethyl sulfoxide (DMSO), 1 µL was added to 200 µL of PRP and incubated at 37˚C for 5 min. To induce platelet aggregation, a solution of ADP (5 µm) or arachidonic acid (1.25 mg/mL) was added to the samples and aggregation was measured using APACT 4004 aggregometer for a 5-minute period. DMSO (0.5% v/v) was used as negative control and indomethacin and aspirin as standard drugs. Platelet aggregation inhibition (%) was calculated by the formula

$$\text{inhibition } \% = \left[1 - \left(D/S\right)\right] \times 100$$

where: *D*, platelet aggregation in the presence of test compounds; *S*, platelet aggregation in the presence of DMSO). Compounds were tested at the initial concentration of 100 µm and IC50 was calculated from log (concentration)-inhibition (%) diagram for those that inhibited the platelet aggregation by 50% or more. IC50 in this test was defined as the concentration at which the test compound inhibits platelet aggregation by 50%.

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