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Efficient Synthesis of a New Class of *N*-Nucleosides of 4*H*-Thiochromeno[2,3-*d*]pyrimidine-10-Sulfone as Potential Anticancer and Antibacterial Agents

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ABSTRACT

A highly practical and efficient preparation of 6-methy-4*H*-thiochromene and 7-methyl-thiochromene[2,3-*d*]pyrimidine derivatives was developed *via* a multi-component reaction of 3-methyl-thiophenol (**1**), aldehydes (**2**), and malononitrile (**3**). A series of pyrimidine nucleoside, thiochromene[2,3-*d*]pyrimidine and thiochromene[2,3-*d*]pyrimidine-10-sulfone was efficiently obtained. These hybrid compounds were evaluated as potential antibacterial and anticancer agents and showed encouraging biological activities. Some of these derivatives showed broad-spectrum antitumour activity against the nine tumour subpanels tested, and demonstrated significant activity in the *in vitro* antitumour screening expressed by MG-MID $\log_{10}GI_{50}$ value of −4.55, −4.67 and −4.73 of compounds **9a**, **9b** and **9c**, respectively.

Keywords: Thiochromene; Pyrimidine; Antibacterial; Anticancer Agents

1. Introduction

Derivation of thiopyranopyrimidine and pyrimidine nucleosides has attracted much attention because of potent antitumor and antiviral activity [1]. Pyrimidine nucleosides substituted at the C-5 position constitute a class of biologically significant molecules [2]. The well-known cancer chemotherapeutic 5-fluorouracil and antiviral agents, such as 5-iodo-2'-deoxyuridine and 5-(trifluoro methyl)-2'-deoxyuridine, have been in clinical use for several years [3]. Meanwhile, in recent years, there have been significant interests in the potential usages of the C-5-substituted pyrimidine nucleosides in synthetic oligonucleotide probes as a tether site for linking reporter groups to nucleic acids [4]. When the modified nucleosides are incorporated into the duplex B-DNA, C-5-substituents are located in the major groove [5], and so do not disrupt Watson-Crick base pairing. As a result, the methodologies for constructing suitable linker arms and generating bonds to C-5 are important for the synthesis of potential therapeutic agents and synthetic oligonucleotide probes. Therefore, the 5-position of pyrimidine nucleosides has been the target of extensive studies on modifications [1].

Also, 1-benzothiopyran-4-ones are the thioanaloggues of flavones [6] which are a class of naturally occurring pharmacologically active compounds. The thioflavones also exhibit various pharmacological activities [7] such as antimalarial, antimicrobial, and antifungal activity and are useful as potent inhibitors of steroid sulfatase [8]. In general, 4*H*-1-benzothio pyran-4-ones are synthesized by the condensation of thiophenols with ethyl benzoylacetates in polyphosphoric acid, but the yields are low to moderate [9]. The cyclization of ethyl *β*-(aryl thio)-cinnamates, derived from Michael addition of thiophenols to ethyl phenylpropiolates, with stannic chloride or phosphorus pentoxide, methanesulfonic acid, gives 2-phenyl-4*H*-1-benzo-thiopyran-4-ones [10]. However, this method could not be applied for the synthesis of methoxy substituted thioflavones because competitive cyclization into the cinnamyl aromatic ring, rather than the sulfur-bearing ring, occurs when cinnamyl ring is activated by methoxy substituent. The reaction of *S*-aroyl derivatives of thio salicylic acid with *N*-phenyl-(triphenylphosphoranylidene) ethemine [11] or (trimethylsilyl)-methylene-triphenylphosphorane [12] leads to the acylphosphoranes which

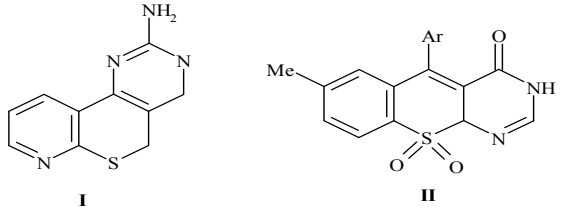
undergo subsequent intramolecular Wittig cyclization to afford 2-phenyl-4*H*-1-benzothiopyran-4-ones, but the separation of phenyl isocyanate is tedious. Alternatively, the condensation of methyl thiosalicylate with trilithiated acetoacetanilides [13] or dilithiated *N*-benzoyl hydrazones [14] with excess lithium diisopropylamide gives the *C*-acylated intermediates which undergo subsequent cyclo-dehydration and hydrolysis with HCl to afford 2-phenyl-4*H*-1-benzothiopyran-4-ones in moderate to high yields. With the aim to develop and identify novel active compounds, we carried out a number of modifications on the structure of organic reagents.

I was devoid of any activity [15], first obtaining the planer isosteric derivative II (**Figure 1**). Also, as a part of our research program devoted to the preparation and evaluation of new anticancer agents, we extensively studied several polycyclic chromophores [16-19] among which we recently disclosed that the pyrido [2,3-*d*] pyrimidine, pyrimido-quinolines, thieno [2,3-*d*] pyrimidine and triazolo [4,3-*a*] pyrimidin-6-sulfonamide showed a detectable cytotoxic activity on human tumor cell lines which was ascribed to its ability to interfere with mitochondrial functions.

2. Chemistry

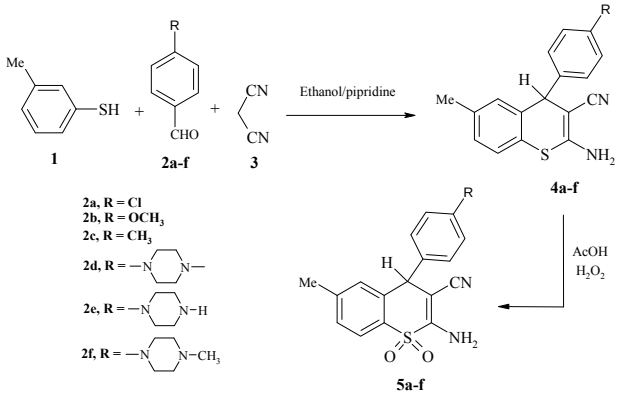
In this paper, we describe a new efficient synthesis of 2-amino-3-cyano-4*H*-thiochromene-4-aryl **4** via cyclocondensation of arylidenemalononitriles (aldehyde + malono nitrile) with 3-methyl-thio-phenol in high yields under the mild conditions, in which the thiopyran moiety gave us the potential to insert a pendant amino and cyano groups both at the 2- and in the 3-position of the chromophore. The reactivity of the new derivatives towards the organic reagents such as formic acid has been studied. The preparation of the thiochromene and the 4-aryl substituted derivatives were performed following the synthetic route described in **Scheme 1**. The starting 2-amino-4-(4-aryl)-6-methyl-4*H*-thiochromeno-3-carbonitrile (**4a-f**) were prepared by the following described procedure via the condensation of thiophenol derivatives **1** with aldehydes and malononitrile 3 in ethanol/piperidine [19].

The compounds were purified by recrystalization and Characterized by analytical and spectral data. In particular, the most discriminating features of the ^{1}H NMR



I II

Figure 1. The planer isosteric derivative I, II.

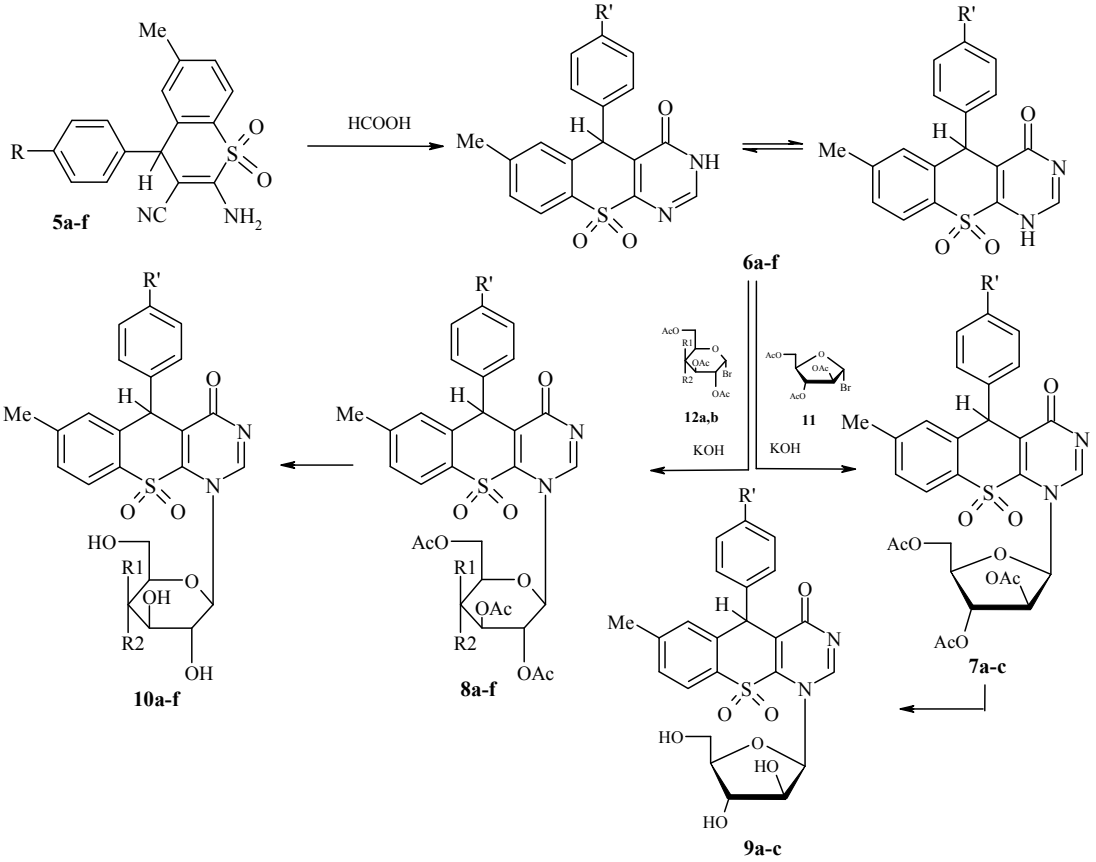


Scheme 1. Synthesis of the starting materials.

spectra of compounds **6a-f** was a singlet at ≈4.50 ppm attributed to the proton in the 4-position of the thiopyran, also at ≈8.80 ppm the resonated proton of the pyrimidine at 2-position.The synthetic sequence leading to the N-glycosides substituted thiochormen [2,3-*d*] pyrimidine (**Scheme 2**) involved the conversion of the pyrimidine moiety of (6a-f) into the intermediate potassium salt, in which the reactive NH functionality was protected as previously reported by us [16]. The subsequent addition of potassium salt of 6 with the appropriate bromo furanosyl/pyranosyl, in anhydrous acetone at room temperature, involves the removing of KBr as a first step **Scheme 2**.

The glycosylation of **6d-f** with 2,3,5-tri-O-acetyl-*β*-*D*-arabinopyranosyl bromide **11** or 2,3,4,6-tetra-O-acetyl -*α*-*D*-glycosyl bromide **12a,b** in acetone and in the presence of aqueous potassium hydroxide afforded the corresponding acetylated nucleosides **7a-c**, **8a-f** respectively in good yields ≈65% - 70% **Scheme 2**. Thin layer chromatography (chloroform: methanol, 8:2) indicated the formation of the pure compounds. The structures of **7a-c**, **8a-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 **8a** as an example, showed the anomeric proton of the glucose moiety as a doublet at δ 5.95 ppm with a coupling constant $J_{1'\text{-}2'}$ = 10.67 Hz indicating *β*-configuration of the anomeric center. The other protons of the glucopyranose ring resonated around δ 3.98 - 5.19 ppm, while the four acetoxy groups appeared as four singlets at δ 1.94, 2.02, 2.11 and 2.14 ppm. The ^{13}C.NMR revealed the signals at δ 166.9 for CO-imide and at δ 169.3, 170.2, 171.3, 171.9 ppm for four acetoxy groups, signals at δ 60.21, 65.23, 67.70, 69.35, 75.34 and 87.19 ppm are assigned to C-6', C-3', C-2', C-4', C-5' and C-1' respectively.

Also, the four signals around δ 22.12 - 22.55 ppm are assigned to the acetate methyl carbon atoms. Deacetylation of acetylated nucleosides **7a-c**, **8a-f** using saturated solution of ammonia in methanol at room temperature afforded the corresponding deacetylated nucleosides **9a-c**,



Scheme 2. Synthesis of the nucleosides of thiochromen derivatives.

10a-f respectively. The structures of free nucleosides **9** and **10** have been established on the basis of their spectral data and elemental analyses. Thus, the ^{1}H NMR spectrum of **10a** showed the anomeric proton as a doublet at δ 6.04 ppm, $J_{1'-2'}$ = 10.61 Hz indicating a *β-D*-configuration. The signals of the other six glucose protons appeared around δ 3.87 - 5.13 ppm, while the signals that disappear on rapid exchange with D_2O are observed at δ 4.60, 5.04, 5.18 and 5.57 ppm, were assigned as the four hydroxyl groups.

3. Results and Discussions

3.1. Antibacterial Activity

The compounds **9a-c**, **10a-f** was evaluated for their efficacy as antibacterial *in vitro* by disc diffusion method against various bacterial strains. The antibacterial activity has been compared to some standard antibacterial agents like sulfanilamide and sulfadiazine that contain a *p*-amino benzene sulfonamide moiety. From the results in **Table 1** Compound **(9a-c)** exhibited excellent activity toward Gram(+ve) and Gram(−ve) bacteria *E. coli*, *P.aeruginosa*, *S. epidermidis*, *B. subtilis* and Vibrio species, as compared with the reference drug (sulfa-diazine, This may be due to the presence of 4-methyl-piprazine on *p*-positions of 4-thiochromene ring and arabinofuranos ring at *N*-1of the pyrimidine, while the other compounds exhibited mild to moderate activity compared to sulfadiazine against *B. subtilis*. All of compounds exhibited excellent activity toward Vibrio species. Compounds **10a, 10d** exhibited high activity toward *Pseudomonos aeruginosa* while the other compounds exhibited mild to moderate activity. Also all of compounds exhibited excellent activity toward *E. coli* as compared with the reference drug (sulfadiazine) (**Table 2**).

3.2. Antitumour Activity

Amongst the substituted 4-piperazino/morpholine-N-nucleoside thiochromene derivatives synthesized, compounds **9a-c** and **10a-f** were chosen by National Cancer Institute (NCI) as prototypes for preliminary test and were evaluated in three cell lines one dose prescreen [20-22] comprising of MCF-7 (breast), NCI-H460 (lung) and SF-268 (CNS) cell lines. These have been in use by DTP (Development Therapeutic Program) for several years to evaluate combinatorial libraries and have proven to be an effective test of agents, which exhibited some capability level to inhibit the growth of human tumour cells in culture. The compounds were added at a single

Table 1. Substituation of the thiochromen nucleosides.

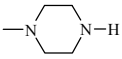
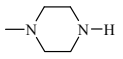
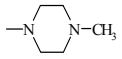
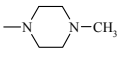
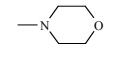
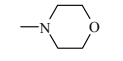
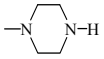
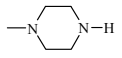
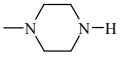
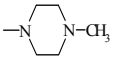
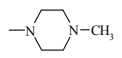
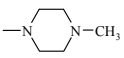
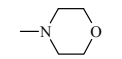
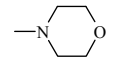
NO.	R	NO.	R'	R1	R2	NO.	R'
5,6a	Cl	**8,10a**		H	OAc/OH	**7a**	
5,6b	OCH_3	**8,10b**		H	OAc/OH	**7b**	
5,6c	CH_3	**8,10c**		H	OAc/OH	**7c**	
5,6d		**8,10d**		OAc/OH	H	**9a**	
5,6e		**8,10e**		OAc/OH	H	**9b**	
5,6f		**8,10f**		OAc/OH	H	**9c**	

Table 2. *In vitro* antibacterial activity of 4*H*-thiochromen[2,3-*d*]pyrimidine nucleosides (9a-c), (10a-f).

Comp.	MIC (lg/mL)				
	E. coli[a] MTCC 448	*P. aeruginosa*[a] MTCC 424	*S. epidermidis*[b] MTCC 435	*B. subtilis*[b] MTCC 441	Vibrio species[a]
9a	18	>25	21	19	21
9b	20	>25	21	18	20
9c	18	>25	22	17	18
10a	15	>25	21	9	20
10b	16	>25	14	9	23
10c	20	>25	17	15	14
10d	13	>25	20	10	22
10e	15	>25	17	8	19
10f	20	>25	19	16	22
SA	>128	>512	>512	>128	>512
SZ	15	22	20	18	13

SA, sulfanilamide, SZ, sulfadiazine, [a]Gram-negative, [b]Gram-positive.

concentration (10^{-4} M) and the culture was incubated for 48 h. End point determination were Compounds **9a**, **9b** and **9c** were further evaluated at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M against 60 different human tumour cell lines organized in subpanels representing melanoma, leukaemia and cancers of breast, prostate, lung, colon, ovary, **CNS** and kidney. The details of the cell lines used are shown in **Table 3** and the experimental procedures have been described in the literature in detail [23-25]. Three dose response parameters were calculated for each experimental agent: the compound concentration required to carry 50% of net cell growth (GI_{50}) which signifies the growth inhibitory power of the test agents, the compound concentrations resulting in total growth inhibition (**TGI**) which signifies the cytostatic effect of the test agent, and the concentration of the compound leading to the 50% of net cell death (LC_{50}) which signifies the cytotoxic effect of the test agent. The $\log_{10}GI_{50}$, $\log_{10}TGI$ and $\log_{10}LC_{50}$ were then determined defined as the means of the $\log_{10}$'s of the individual GI_{50}, **TGI** and LC_{50} value as shown in **Table 3**, respectively. Compounds having $\log_{10}GI_{50}$ values −4 and <−4 were declared to be active. The mean graph points (MG-MID) represent average values for each of the mentioned parameters and indicate the average sensitivity of all cell lines to each tested compound.

Made with a protein binding dye, sulforhodamine B (SRB). Results for each compound were reported as per centage test cell growth compared with untreated control cells (PTC) as illustrated in **Table 2**. Compounds, whi-

Table 3. Primary *in vitro* growth inhibition assay results at 10^{-4} M concentration.

Compound	PTC[a]			60-Tumour cell line selection
	MCF-7[b]	NCI-H460[c]	SF-268[d]	
9a	0	0	0	Y
9b	44	1	34	Y
9c	52	31	60	Y
10a	102	84	106	N
10b	111	62	123	N
10c	99	78	108	N
10d	108	65	118	N
10e	105	81	104	N
10f	100	73	116	N

Y, yes selected, N, not selected. [a]PTC, percent test cell growth compared with untreated control cells. [b]Breast cell line. [c]Lung cell line. [d]CNS cell line.

chreduce the growth of any one of the cell lines to 32% or less, were selected for further evaluation in the full panel of 60 human tumour cell lines. Compound **9a** has shown 0% of growth inhibition against all the three cell lines. Similarly, **9b** and **9c** presented the 1% and 31% of growth inhibition for the NCI-H460 cell line, respectively. However, compounds **10a-f** have not reduced the growth of any cell lines by 32% or less. Therefore, only three compounds **9a**, **9b** and **9c** have been selected for 60-cell line panel assay (**Table 3**).

From **Table 4**, we can conclude that, all the active compounds in this test showed broad-spectrum antitumour activity against the nine tumour subpanels tested, and demonstrated significant activity in the *in vitro* antitumour screening expressed by MG-MID $\log_{10}GI_{50}$ value of −4.55, −4.67 and −4.73 of compounds **9a**, **9b** and **9c**, respectively, whereas compounds **10a-f** were inactive ($\log_{10}GI_{50} > -4$). Substitution of *N*-glucopyranosyl (10a-c) and N-galactopyranosyl (10e-f) on thiochromen [2,3-*d*] pyrimidine ring has reduced the activity. $Log_{10}GI_{50}$ value of compound **9a** is −4.50 and −4.54 in the breast cancer cell lines (MCF-7 and MDA-MB-231, respectively), whereas this value in case of **E**7010 is −6.14 and −5.07 for the same cell lines [25]. Substitution of arabinofuranosyl group on the N-1 position of pyrimidine, and piperazine, 4-methylpiperazine and morpholine at 4 positions of thiochromene, respectively, (**9a-c**) also exhibits similar $\log_{10}GI_{50}$ value for these cell lines, that is, −4.45 and −4.72, however the activity is enhanced particularly in case of leukaemia CCRF-CEM cell line ($\log_{10}GI_{50}$ −5.18, GI_{50} is 6.62 μM). In case of compound **9c** $\log_{10}GI_{50}$ value is −5.36 and −4.38 in the breast cancer cell lines (MCF-7 and MDA-MB-231 cell lines, respectively) and also demonstrated significant activity in other cell lines.

4. Conclusion

The synthesis and screening of anticancer and antibacterial activities of a novel series of N- nucleoside-thiochromene-5-piperazino/5-methyl-piperazino/and or 5-morpholino have been investigated. Compounds **9a-c** were screened against 60 human cancer cell lines and exhibited a broad spectrum of activity against almost all the cancer cell lines and in the case of certain cancer cell lines, the activity was comparable to **E**7010. Furthermore, most of the compounds showed better activity than the controls in antibacterial screening except against *P. aeruginosa*.

5. Experimental

All starting materials, solvents, and reagents were very pure grade. Chromatography solvents were HPLC grade. Reactions were monitored by thin layer chromatography (TLC), (Silica gel 60 F_{254}). Melting points were determined on the Electrothermal 9100 melting point apparatus and are uncorrected. The IR spectra (KBr) were recorded on a FT-IR NEXCES spectrophotometer (Shimadzu, Japan). The NMR spectra were measured with a Jeol ECA 500 MHz. Mass spectra (EI) were run at 70 eV with a Finnigan SSQ 7000 spectrometer. Compounds were properly characterized by elemental analyses. The Pharmacological evaluations of the products were carried out in Pharmacological Unit Pharmacology department, (NCI, Cairo University, Egypt).

Preparation of the 2-amino-4-(4-aryl)-6-methyl-4H-thiochromeno-3-carbonitrile (4a-f), *General procedure*: The solution of each of 3-methylthiopenol (0.13 mol), aldehyde (**2a-f**) (0.01 mol) and malononitrile (0.01 mol) in ethanol absolute (50 ml) and piperidine (1 ml) was heated under reflux for 3 - 5 hours (under TLC control). The reaction mixture was allowed to cool to room temperature, poured into water (100 mL), acidify with acetic acid. The formed solid was collected by filtration, washed with water (50 mL), dried and crystallized from ethanol (100 ml), in 56% - 68% yields.

2-*amino*-4-(4-*chlorophenyl*)-6-*methyl*-4*H*-*thiochromeno*-3-*carbonitrile* (4*a*), It was obtained from **2a**, in 65% yield, as yellow crystals, m. p. 238˚C - 240˚C, IR (cm^{-1}, ν), 3440 (br, NH), 2212 (CN), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.29 (s, CH_3), 4.39 (s, thiopyran-*H*), 7.00 (m, Ar-*H*), 7.06 (m, Ar-*H*), 7.08 (s, Ar-*H*), 7.11 (m, Ar-*H*), 7.18 (d, 2H, Ar-*H*), 7.82 (d, 2H, Ar-*H*) 9.85 (br, NH, D_2O exchangeable), ^{13}C.NMR: 22.34 (*C*H$_3$), 39.28 (*C*-thiopyran-4), 117.9 (*C*N), 125.5-140.8 (12*C*-*Ar*), 141.2, 143.9 (2*C*-thiopyran), Its MS (m/z), 312 (M^+, 72%), 313 ($M^+ + 1$, 19%), $C_{17}H_{13}ClN_2S$ (312.8).

2-*amino*-4-(4-*methoxyphenyl*)-6-*methyl*-4*H*-*thiochromeno*-3-*carbonitrile* (4*b*), It was obtained from **2b**, in

Table 4. Inhibition of *in vitro* cancer cell lines by selected 4*H*-thiochromen[2,3-*d*]-pyrimidine nucleosides 9a-c[a].

Panel cell line	Response parameters: (A) log_{10}GI50 b (M), (B) log_{10}TGIc (M), (C) log_{10}LC50 d (M) and MG_MIDe								
	Compound 9a			Compound 9b			Compound 9c		
	A	B	C	A	B	C	A	B	C
Non-small cell lung cancer									
A549/ATCC	−4.67	−4.39	−4.01	−4.61	−4.15	>−4.00	−4.49	>−4.00	>−4.00
EKVX	−4.53	>−4.00	>−4.00	−4.58	>−4.00	>−4.00	−4.31	>−4.00	>−4.00
HOP-62	−4.51	−4.07	>−4.00	−4.78	−4.42	−4.07	>−4.00	>−4.00	>−4.00
HOP-92	−4.81	−4.44	−4.07	−4.83	−4.39	>−4.00	>−4.00	>−4.00	>−4.00
NCI-H226	−4.53	−4.01	>−4.00	−4.62	−4.23	>−4.00	−4.37	>−4.00	>−4.00
NCI-H322M	−4.51	>−4.00	>−4.00	−4.83	−4.39	>−4.00	>−4.00	>−4.00	>−4.00
NCI-H460	−4.50	>−4.00	>−4.00	−4.45	−4.00	>−4.00	−5.33	>−4.00	>−4.00
NCI H522	nt	nt	nt	nt	nt	nt	−5.19	>−4.00	>−4.00
Leukaemia									
CCRF-CEM	−4.68	>−4.00	>−4.00	−5.18	>−4.00	>−4.00	−4.67	>−4.00	>−4.00
HL-60 (TB)	−4.60	−4.21	>−4.00	−4.62	−4.35	−4.08	−5.01	>−4.00	>−4.00
K-562	−4.70	−4.08	>−4.00	−4.89	−4.59	−4.30	−5.07	>−4.00	>−4.00
MOLT-4	−4.64	>−4.00	>−4.00	−4.71	−4.24	>−4.00	−4.30	>−4.00	>−4.00
RPMI-8226	nt	Nt	Nt	−4.75	−4.27	>−4.00	−4.54	>−4.00	>−4.00
SR	−4.64	−4.17	>−4.00	−4.83	−4.42	−4.01	−5.20	>−4.00	>−4.00
Colon cancer									
COLO 205	−4.79	−4.29	>−4.00	−4.92	−4.61	−4.31	−4.99	−4.24	>−4.00
HCC-2998	−4.52	>−4.00	>−4.00	−4.87	−4.54	−4.21	−5.08	>−4.00	>−4.00
HCT-116	−4.55	>−4.00	>−4.00	−4.81	−4.54	−4.27	−5.14	>−4.00	>−4.00
HCT-15	−4.57	>−4.08	>−4.00	−4.48	>−4.00	−4.00	−4.86	>−4.00	>−4.00
HT29	−4.66	−4.24	>−4.00	−4.64	−4.27	>−4.00	−5.40	>−4.00	>−4.00
KM12	−4.64	−4.31	>−4.00	−4.86	−4.54	−4.23	−5.38	>−4.00	>−4.00
SW-620	−4.54	>−4.00	>−4.00	−4.55	>−4.00	>−4.00	−5.12	>−4.00	>−4.00
Breast cancer									
MCF-7	−4.50	>−4.00	>−4.00	−4.45	>−4.00	>−4.00	−5.36	>−4.00	>−4.00
NCI/ADR-RES	−4.40	>−4.00	>−4.00	−4.63	−4.12	>−4.00	nt	>−4.00	>−4.00
MDA-MB-231/ATCC	−4.54	>−4.00	>−4.00	−4.72	−4.30	>−4.00	−4.38	nt	nt
HS 578T	−4.55	>−4.00	>−4.00	−4.75	−4.38	−4.01	−4.62	>−4.00	>−4.00
MDA-MB-435	−4.07	>−4.00	>−4.00	−4.56	−4.09	>−4.00	−5.49	>−4.00	>−4.00
BT-549	−4.44	−4.00	>−4.00	−4.78	−4.64	−4.14	−4.60	>−4.00	>−4.00
T-47D	−4.73	>−4.01	>−4.00	−4.97	−4.29	>−4.00	−5.20	>−4.00	>−4.00
MG_MID	−4.55	−4.10	−4.01	−4.67	−4.23	−4.03	−4.73	−4.01	−4.01
Melanoma									

Continued

LOX IMVI	−4.49	>−4.00	>−4.00	−4.68	−4.33	>−4.00	−4.62	>−4.00	>−4.00
MALME 3M	−4.46	>−4.00	>−4.00	−4.95	−4.46	>−4.00	>−4.00	>−4.00	>−4.00
M14	−4.33	>−4.00	>−4.00	−4.72	−4.41	−4.10	−4.94	>−4.00	>−4.00
SK-MEL-2	−4.37	>−4.00	>−4.00	−4.73	−4.37	−4.01	nt	nt	nt
SK-MEL-28	−4.05	>−4.00	>−4.00	−4.45	>−4.00	>−4.00	−4.63	>−4.00	>−4.00
SK-MEL-5	−4.60	−4.07	>−4.00	−4,85	−4.53	−4.21	−5.25	>−4.00	>−4.00
UACC-257	−4.93	−4.28	>−4.00	−4.64	−4.22	>−4.00	−4.05	>−4.00	>−4.00
UACC-62	−4.34	>−4.00	>−4.00	−4.66	−4.12	>−4.00	−5.05	>−4.00	>−4.00

[a]Data obtained from the NCI's *in vitro* disease-oriented human tumour cells screen. [b]$Log_{10}GI_{50}$ = log of molar concentration that inhibits 50% net cell growth. [c]$Log_{10}TGI$ = log of molar concentration that produces a total growth inhibition. [d]$Log_{10}LC_{50}$ = log of molar concentration that leads to 50% net cell death. [e]MG-MID = mean graph midpoint = arithmetical mean value for all tested cell lines

67% yield, as white powder, m. p. 219˚C - 221˚C, IR (cm^{-1}, *v*), 3315 (br, NH), 2215 (CN), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.29 (s, CH_3), 3.78 (s, OCH_3), 4.42 (s, thiopyran-*H*), 6.95 (m, Ar-*H*), 7.02 (m, Ar-*H*), 7.07 (s, Ar-*H*), 7.12 (m, Ar-*H*), 7.28 (d, 2H, Ar-*H*), 7.96 (d, 2H, Ar-*H*), 10.05 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 21.89 (CH_3), 41.32 (*C*-thiopyran-4), 57.42 (OCH_3), 118.2 (*C*N), 121.9-141.3 (12*C*-*Ar*), 141.9, 144.2 (2*C*-thiopyran), Its MS (m/z), 308 (M^+, 100%), $C_{18}H_{16}N_2OS$ (308.4).

.1.3. 2-*amino*-4-(4-*methylphenyl*)-6-*methyl*-4*H*-*thiochromeno*-3-*carbonitrile* (4*c*), It was obtained from **2c**, in 64% yield, as white crystals, m. p. 202˚C - 204 ˚C, IR (cm^{-1}, *v*), 3280 (br, NH), 2217 (CN), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.29 (s, CH_3), 2.38 (s, CH_3), 4.48 (s, thiopyran-*H*), 6.98 (m, Ar-*H*), 7.03 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.13 (m, Ar-*H*), 7.32 (d, 2H, Ar-*H*), 7.95 (d, 2H, Ar-*H*), 9.75 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 21.9 (CH_3), 24.54 (CH_3), 41.37 (*C*-thiopyran-4), 118.7 (*C*N), 120.7-141.1 (12*C*-*Ar*), 142.9, 144.7 (2*C*-thiopyran), Its MS (m/z), 292 (M^+, 68%), $C_{18}H_{16}N_2S$ (292.4).

2-*amino*-6-*methyl*-4-(4-*piperazin*-1-*ylphenyl*)-4*H*-*thiochromeno*-3-*carbonitrile* (4*d*), It was obtained from **2d**, in 59% yield, as brown crystals, m.p. 179˚C - 181˚C, IR (cm^{-1}, *v*), 3370 (br, NH), 2220 (CN), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.26 (s, CH_3), 2.56 (m, 4H, $N(CH_2)_2$), 3.03 (m, 4H, $HN(CH_2)_2$), 4.56 (s, thiopyran-*H*), 7.01 (m, Ar-*H*), 7.04 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.14 (m, Ar-*H*), 7.26 (d, 2H, Ar-*H*), 8.05 (d, 2H,Ar-*H*), 9.65, 10.15 (2brs, D_2O exchangeable-N*H*), ^{13}C.NMR: 25.12(CH_3), 38.76 (*C*-thiopyran-4), 43.5 (2C, $HN(CH_2)_2$), 47.6 (2C, $N(CH_2)_2$), 116.8(*C*N), 120.9 - 139.7(12*C*-*Ar*), 141.3, 145.1(2*C*-thio pyran), Its MS (m/z), 362 (M^+, 43%), $C_{21}H_{22}N_4S$ (362.5).

2-*amino*-6-*methyl*-4-[4-(4-*methylpiperazin*-1-*yl*)*phenyl*]-4*H*-*thiochromeno*-3-*carbonitrile* (4*e*), It was obtained from **2e**, in 61% yield, as yellow crystals, m. p. 193˚C - 195˚C, IR (cm^{-1}, *v*), 3260 (br, NH), 2215 (CN), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.21 (s, CH_3), 2.29 (s, 3H, CH_3), 2.56 (m, 4H, $N(CH_2)_2$), 2.68 (m, 4H, $N(CH_2)_2$), 4.51 (s, thiopyran-*H*), 6.98 (m, Ar-*H*), 7.03 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.15 (m, Ar-*H*), 7.21 (d, 2H, Ar-*H*), 8.01 (d, 2H, Ar-*H*), 9.80 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 22.36 (CH_3), 39.83 (*C*-thiopyran-4), 46.01 (N-CH_3), 47.8 (2C, $N(CH_2)_2$), 52.7 (2C, $N(CH_2)_2$), 114.7 (*C*N), 118.7 - 139.3 (12*C*-*Ar*), 140.5, 144.3 (2*C*-thiopyran), Its MS (m/z), 376 (M^+, 51%), $C_{22}H_{24}N_4S$ (376.5).

2-*amino*-6-*methyl*-4-(4-*morpholin*-4-*ylphenyl*)-4*H*-*thiochromeno*-3-*carbonitrile* (4*f*), It was obtained from **2f**, in 58% yield, as brown powder, m. p. 211˚C - 213˚C, IR (cm^{-1}, *v*), 3290 (br, NH), 2213 (CN), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.28 (s, CH_3), 2.55 (m, 4H, $N(CH_2)_2$), 3.58 (m, 4H, $O(CH_2)_2$), 4.52 (s, thiopyran-*H*), 7.04 (m, Ar-*H*), 7.07 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.16 (m, Ar-*H*),7.23 (d, 2H, Ar-*H*), 8.12 (d, 2H, Ar-*H*), 9.60 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 23.49 (CH_3), 40.13 (*C*-thiopyran-4), 46.5 (2C, $N(CH_2)_2$), 65.8 (2C, $O(CH_2)_2$), 117.6 (*C*N), 119.9 - 140.3 (12*C*-*Ar*), 142.1, 145.3 (2*C*-thiopyran), Its MS (m/z), 363 (M^+, 65%), $C_{21}H_{21}N_3OS$ (363.5).

Preparation of the 2-amino-4-(4-aryl)-6-methyl-4H-thiochromeno-3-carbonitrile-1,1-dioxide (5a-f), ***General procedure*:** The solution of **4a-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 (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 proper solvent.

2-*amino*-4-(4-*chlorophenyl*)-6-*methyl*-4*H*-*thiochromeno*-3-*carbonitrile*-1,1-*dioxide* (5*a*), It was obtained from **4a**, in 62% yield, as yellow crystals, m. p. 251˚C - 253˚C, IR (cm^{-1}, *v*), 3280 (br, NH), 2215 (CN),1340 (SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.30 (s, CH_3), 4.42 (s, thiopyran-*H*), 7.02 (m, Ar-*H*), 7.07 (m, Ar-*H*), 7.11 (s, Ar-*H*), 7.13 (m, Ar-*H*), 7.23 (d, 2H, Ar-*H*), 7.90 (d, 2H, Ar-*H*), 10.05 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 24.20 (CH_3), 40.08 (*C*-thiopyran-4), 116.9 (*C*N), 123.5 - 140.6 (12*C*-*Ar*), 141.6, 143.4 (2*C*-thiopyran), Its MS

(m/z), 344 (M^+, 65%), 313 ($M^+ + 1$, 20%), $C_{17}H_{13}ClN_2O_2S$ (344.8).

2-*amino*-4-(4-*methoxyphenyl)*-6-*methyl*-4*H*-*thiochrome no*-3-*carbonitrile*-1,1-*dioxide* (5*b*), It was obtained from **4b**, in 56% yield, as white powder, m. p. 243˚C - 245˚C, IR (cm^{-1}, *v*), 3305 (br, NH), 2212 (CN), 1324 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.32 (s, CH_3), 3.86 (s, OCH_3), 4.40 (s, thiopyran), 6.98 (m, Ar-*H*), 7.04 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.15 (m, Ar-*H*), 7.27 (d, 2H, Ar-*H*), 7.95 (d, 2H, Ar-*H*), 9.45 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 23.61 (*C*H_3), 40.45 (*C*-thiopyran-4), 58.26 (O*C*H_3), 117.6 (*C*N), 120.6 - 141.5 (12*C*-*Ar*), 141.3, 144.5 (2*C*-thiopyran), Its MS (m/z), 340 (M^+, 83%), $C_{18}H_{16}N_2O_3S$ (340.4).

2-*amino*-4-(4-*methylphenyl)*-6-*methyl*-4*H*-*thiochrome no*-3-*carbonitrile*-1,1-*dioxide* (5*c*), It was obtained from **4c**, in 60% yield, as white crystals, m. p. 253˚C -255˚C, IR (cm^{-1}, *v*), 3315 (br, NH), 2221(CN), 1352 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.28 (s, CH_3), 2.35 (s, CH_3), 4.44 (s, thiopyran), 6.99 (m, Ar-*H*), 7.02 (m, Ar-*H*), 7.08 (s, Ar-*H*), 7.12 (m, Ar-*H*), 7.30 (d, 2H, Ar-*H*), 7.91 (d, 2H, Ar-*H*), 9.90 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 21.92 (*C*H_3), 23.22 (*C*H_3), 40.23 (*C*-thiopyran-4), 118.4 (*C*N), 121.4 - 141.3 (12*C*-*Ar*), 142.5, 144.2 (2*C*-thiopyran), Its MS (m/z), 324 (M^+, 63%), $C_{18}H_{16}N_2O_2S$ (324.4).

2-*amino*-6-*methyl*-4-(4-*piperazin*-1-*ylphenyl*)-4*H*-*thio chromeno*-3-*carbonitrile*-1,1-*dioxide* (5*d*), It was obtained from **4d**, in 59% yield, as colorless crystals, m.p. 219˚C - 221˚C, IR (cm^{-1}, *v*), 3267 (br, NH's), 2214 (CN), 1353 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.28 (s, CH_3), 2.58 (m, 4H, N(CH_2)$_2$), 3.12 (m, 4H, HN(CH_2)$_2$), 4.52 (s, thiopyran-*H*), 7.00 (m, Ar-*H*), 7.05 (m, Ar-*H*), 7.12 (s, Ar-*H*), 7.16 (m, Ar-*H*), 7.24 (d, 2H, Ar-*H*), 8.12 (d, 2H, Ar-*H*), 10.23, 10.50 (2brs, D_2O exchangeable-N*H*), ^{13}C.NMR: 22.47 (*C*H_3), 40.16 (*C*-thiopyran-4), 42.9 (2C, HN(*C*H_2)$_2$), 47.8 (2C, N(*C*H_2)$_2$), 118.3(*C*N), 121.4 - 140.6 (12*C*-*Ar*), 141.6, 145.7 (2*C*-thiopyran), Its MS (m/z), 394 (M^+, 51%), 395 ($M^+ + 1$, 13%), $C_{21}H_{22}N_4O_2S$ (394.5).

2-*amino*-6-*methyl*-4-[4-(4-*methylpiperazin*-1-*yl*)*phen yl]*-4*H*-*thiochromeno*-3-*carbonitrile*-1,1-*dioxide* (5*e*), It was obtained from **4e**, in 63% yield, as yellow crystals, m. p. 231˚C - 233˚C, IR (cm^{-1}, *v*), 3256 (br, NH), 2214 (CN), 1320 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.25 (s, CH_3), 2.43 (s, CH_3), 2.56 (m, N(CH_2)$_2$), 2.68 (m, N(CH_2)$_2$), 4.51 (s, thiopyran-*H*), 6.98 (m, Ar-*H*), 7.03 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.15 (m, Ar-*H*), 7.21 (d, 2H, Ar-*H*), 8.01 (d, 2H, Ar-*H*), 9.80 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 23.25 (*C*H_3), 39.83 (*C*-thiopyran-4), 46.01 (N-*C*H_3), 47.8 (2C, N(*C*H_2)$_2$), 52.7(2C, N(*C*H_2)$_2$), 114.7 (*C*N), 118.7 - 139.3(12*C*-*Ar*), 140.5, 144.3 (2*C*- thiopyran), Its MS (m/z), 376 (M^+, 51%), $C_{22}H_{24}N_4O_2S$ (376.5).

2-*amino*-6-*methyl*-4-(4-*morpholin*-4-*ylphenyl*)-4*H*-*thio chromeno*-3-*carbonitrile*-1,1-*dioxide* (5*f*), It was obtained from **4f**, in 53% yield, as brown powder, m. p. 253˚C -255˚C, IR (cm^{-1}, *v*), 3290 (br, NH), 2213 (CN), 1353 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.25 (s, CH_3), 2.58 (m, 4H, N(CH_2)$_2$), 3.61 (m, 4H, O(CH_2)$_2$), 4.50 (s, thiopyran-*H*), 7.02 (m, Ar-*H*), 7.06 (m, Ar-*H*), 7.11 (s, Ar-*H*), 7.15 (m, Ar-*H*), 7.21 (d, 2H, Ar-*H*), 8.10 (d, 2H, Ar-*H*), 9.65 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 23.49 (*C*H_3), 41.17(*C*-thiopyran-4), 46.51 (2C, N(*C*H_2)$_2$), 65.80 (2C, O(*C*H_2)$_2$), 119.3 (*C*N), 120.3 - 140.8 (12*C*-*Ar*), 142.3, 144.9 (2*C*-thiopyran), Its MS (m/z), 395 (M^+, 53%), $C_{21}H_{21}N_3O_3S$ (395.5).

Preparation of 7-methyl-5-(4-substituted-phenyl)-3, 5-dihydro-*4H*-thiochromeno-[2,3-*d*]pyrimidine-4-one-10,10-dioxide (6a-f). ***General procedure*:** A mixture of compounds **5a-f** (0.01mol), formic acid (10 mL) and catalytic amount of concentrated hydrochloric acid was heated under reflux for 10 - 15 hours (TLC control). The reaction mixture was allowed to cool to room temperature, poured into water (100 mL). The formed solid was collected by filtration, washed with absolute ethanol (50 mL), dried and crystallized from dimethylformamide.

5-(4-*Chlorophenyl*)-7-*methyl*-3,5-*dihydro*-4*H*-*thiochro meno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (6*a*). It was obtained from **5a**, in 76% yield, as yellow powder, m.p. 288˚C - 290˚C, IR (cm^{-1}, *v*), 3240 (br, NH), 1678 (CO), 1330 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.29 (s, CH_3), 4.47 (s, thiopyran-*H*), 6.98 (m, Ar-*H*), 7.05 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.16 (m, Ar-*H*), 7.20 (d, 2H, Ar-*H*), 8.04 (d, 2H, Ar-*H*), 8.84 (s, pyrimidine-*H*), 9.15 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 23.19 (*C*H_3), 40.11 (*C*-thiopyran-4), 123.5 - 143.7 (15*C*-*Ar*), 167.4 (*C*O), Its MS (m/z), 372 (M^+, 87%), 373 ($M^+ + 1$, 23%), $C_{18}H_{13}ClN_2O_3S$ (372.8).

5-(4-*Methoxyphenyl*)-7-*methyl*-3,5-*dihydro*-4*H*-*thio chromeno*[2,3-d] *pyrimidine*-4-*one*-10,10-*dioxide* (6*b*). It was obtained from **5b**, in 76% yield, as white powder, m. p. 278˚C - 280˚C, IR (cm^{-1}, *v*), 3270 (br, NH), 1685 (CO), 1345 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.30 (s, CH_3), 3.84 (s, OCH_3), 4.39 (s, thiopyran-*H*), 7.00 (m, Ar-*H*), 7.03 (m, Ar-*H*), 7.11 (s, Ar-*H*), 7.17 (m, Ar-*H*), 7.29 (d, 2H, Ar-*H*), 7.87 (d, 2H, Ar-*H*), 8.78 (s, pyrimidine-*H*) 10.05 (br,D_2O exchangeable-N*H*), ^{13}C.NMR: 23.61 (*C*H_3), 59.18 (O*C*H_3), 119.8 - 146.5 (15*C*-*Ar*), 166.9 (*C*O), Its MS (m/z), 368 (M^+, 61%), $C_{19}H_{16}N_2O_4S$ (368.4).

5-(4-*Methylphenyl*)-7-*methyl*-3,5-*dihydro*-4*H*-*thiochro meno*[2,3-d]*pyrimidine*-4-*one*-10,10-*dioxide* (6*c*). It was obtained from **5c**, in 75% yield, as white powder, m.p. 301˚C - 303˚C, IR (cm^{-1}, *v*), 3276 (br, NH), 1678 (CO), 1343 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.24 (s, CH_3), 2.31 (s, CH_3), 4.38 (s, thiopyran-*H*), 6.96 (m, Ar-*H*), 7.01 (m, Ar-*H*), 7.06 (s, Ar-*H*), 7.11 (m, Ar-*H*), 7.28 (d, 2H, Ar-*H*), 7.96 (d, 2H, Ar-*H*), 8.79 (s, pyrimidine-*H*), 10.35

(br, D_2O exchangeable-N*H*), ^{13}C.NMR: 21.49 (*C*H_3), 24.21 (*C*H_3), 43.13(*C*-thiopyran-4), 121.6 - 146.8 (15*C*-*Ar*), 168.5 (*C*O), Its MS(m/z), 352 (M^+, 71%), $C_{19}H_{16}N_2O_3S$ (352.4).

7-*methyl*-5-(4-*piperazin*-1-*ylphenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*-[2,3-*d*]-*pyrimidine*-4-*one*-10,10-*dioxide* (6*d*). It was obtained from **5d**, in 65% yield, as white crystals, m. p. 263˚C - 265˚C, IR (cm^{-1}, *v*), 3335 (br, NH's), 1687 (CO), 1339 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.30 (s, C*H*$_3$), 2.54 (m, 4H, N(C*H*$_2$)$_2$), 3.09 (m, 4H, HN(C*H*$_2$)$_2$), 4.45 (s, thiopyran-*H*), 7.02 (m, Ar-*H*), 7.07 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.26 (d, 2H, Ar-*H*), 8.00 (d, 2H, Ar-*H*), 8.93 (s, pyrimidine-*H*), 10.20, 10.65 (2brs, D_2O exchangeable-N*H*), ^{13}C.NMR: 21.97 (*C*H$_3$), 40.07 (*C*-thiopyran-4), 43.5 (2C, HN(*C*H$_2$)$_2$), 46.9 (2C, N(*C*H$_2$)$_2$), 120.5 - 145.9 (15*C*-*Ar*), 167.8 (*C*O), Its MS (m/z), 422 (M^+, 43%) , $C_{22}H_{22}N_4O_3S$ (422.4).

7-*Methyl*-5-[4-(4-*methylpiperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (6*e*). It was obtained from **5e**, in 71% yield, as yellow crystals, m. p. 271˚C -273˚C, IR (cm^{-1}, *v*), 3258 (br, NH), 1685 (CO), 1337(SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.23 (s, C*H*$_3$), 2.41 (s,C*H*$_3$), 2.54 (m, N(C*H*$_2$)$_2$), 2.66 (m, N(C*H*$_2$)$_2$), 4.47 (s, thiopyran-*H*), 6.99(m, Ar-*H*), 7.05 (m, Ar-*H*), 7.12(s, Ar-*H*),7.17(m, Ar-*H*), 7.24 (d, Ar-*H*), 7.96 (d, Ar-*H*), 8.85 (s, pyrimidine-*H*), 10.45 (br, D_2O exchangeable-N*H*), ^{13}C. NMR: 21.35 (*C*H$_3$), 39.92 (*C*-thiopyran-4), 45.89 (N-*C*H$_3$), 48.21 (2C, N(*C*H$_2$)$_2$, 53.67 (2C, N(*C*H$_2$)$_2$), 119.8 - 147.6 (15*C*-*Ar*), 167.5(*C*O), Its MS (m/z), 376 (M^+, 51%), $C_{23}H_{24}N_4O_3S$ (436.4).

7-*Methyl*-5-(4-*morpholin*-1-*ylphenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]-*pyrimidine*-4-*one*-10,10-*dioxide* (6*f*). It was obtained from **5f**, in 65% yield, as yellow powder, m. p. 303˚C - 305˚C, IR (cm^{-1}, *v*), 3268 (br, NH), 1678 (CO), 1348 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.22 (s, C*H*$_3$), 2.55 (m, 4H, N(C*H*$_2$)$_2$), 3.64 (m, 4H, O(C*H*$_2$)$_2$), 4.53 (s, thiopyran-*H*), 7.00 (m, Ar-*H*), 7.04 (m, Ar-*H*), 7.09 (s, Ar-*H*), 7.13 (m, Ar-*H*), 7.20 (d, 2H, Ar-*H*), 8.02 (d, 2H, Ar-*H*), 8.93 (s, pyrimidine-*H*), 9.95 (br, D_2O exchangeable-N*H*), ^{13}C.NMR: 22.89 (*C*H$_3$), 43.26 (*C*-thiopyran-4), 45.91 (2C, N(*C*H$_2$)$_2$), 64.92 (2C, O(*C*H$_2$)$_2$), 120.6 - 147.8 (15*C*-*Ar*), 166.8 (*C*O), Its MS (m/z), 423 (M^+, 65%), $C_{22}H_{21}N_3O_4S$ (423.4).

Preparation of the acetylated N-nucleosides of 3, 5-dihydro-4*H*-thiochromeno[2,3-*d*]pyrimidine-4-one-10,10-dioxide (7a-c) and (8a-f), *General procedure*: To a solution of **6d-f** (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 (**11**) or 2,3,4,6-tetra-*O*-acetyl-α-D-gluco-/or galactopyranosyl bromide (**12a,b**) (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 filtered off and washed with distilled water to remove KBr formed. The product was dried, and crystallized from the proper solvent.

***N*-(2',3',5'-*tri*-*O*-*acetyl*-*β*-*D*-*arabinofuranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thiochrom eno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (7*a*).** It was obtained from **6d** and 2,3,5-tri-*O*-acetyl-*α*-*D*-arabino furanosyl)-bromide (**11**), as white powder, m. p. 209˚C - 211˚C, IR (cm^{-1}, *v*), 3260 (br, NH), 1741 (3CO), 1686 (CO), 1330 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 1.95, 1.99, 2.01 (3s, 3C*H*$_3$CO), 2.31 (s, C*H*$_3$), 2.45 (m, 4H, N(C*H*$_2$)$_2$), 3.03 (m, 4H, HN(C*H*$_2$)$_2$), 4.08 (m, *H*-4'), 4.15 (m, *H*-5', *H*-5''), 4.48 (s, thiopyran-*H*), 5.31 (m, *H*-3'), 5.38 (m, *H*-2'), 6.73 (d, *J* = 3.67 Hz, *H*-1'), 7.04 (m, Ar-*H*), 7.11 (m, H, Ar-*H*), 7.15 (s, Ar-*H*), 7.21 (m, Ar-*H*), 7.30 (d, 2H, Ar-*H*), 8.00 (d, 2H, Ar-*H*), 8.86 (s, pyrimidine-*H*), 10.25 (br, NH), ^{13}C. NMR: 21.43 (*C*H$_3$), 22.19, 22.24, 22.61 (3*C*H$_3$), 39.83 (*C*-thiopyran-4), 43.71 (2C, HN(*C*H$_2$)$_2$), 45.93 (2C, N(*C*H$_2$)$_2$), 61.52 (*C*-5'), 66.23 (*C*-3'), 66.78 (*C*-2'), 67.37 (*C*-4'), 85.73 (*C*-1'), 121.3 - 147.5 (15*C*-*Ar*), 167.8 (*C*O), 169.2, 170.5, 172.6 (3*C*O), Its MS (m/z), 680 (M^+, 28%), $C_{33}H_{36}N_4O_{10}S$ (680.7).

***N*-(2',3',5'-*tri*-*O*-*acetyl*-*β*-*D*-*arabinofuranosyl*)-7-*methyl* -5-[4-(4-*methylpiperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (7*b*).** It was obtained from compound **6e** and 2,3,5-tri-*O*-acetyl-*α*-*D*-arabinofuranosyl)-bromide (**11**), as pale yellow powder, m. p. 219˚C - 221˚C, IR (cm^{-1}, *v*), 1737 (3CO), 1679 (CO), 1341 (SO), ^{1}H.NMR(DMSO- d_6, δ, ppm): 1.92, 1.97, 2.03 (3s, 3C*H*$_3$CO), 2.24 (s, C*H*$_3$), 2.28 (s, C*H*$_3$), 2.53 (m, 4H, N(C*H*$_2$)$_2$), 3.11 (m, 4H, HN(C*H*$_2$)$_2$), 4.05 (m, *H*-4'), 4.12 (m, *H*-5', *H*-5''), 4.46 (s, thiopyran-*H*), 5.28 (m, *H*-3'), 5.31 (m, *H*-2'), 6.72 (d, *J* = 3.71 Hz, *H*-1'), 7.03 (m, Ar-*H*), 7.09 (m, Ar-*H*), 7.14 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.25 (d, Ar-*H*), 8.01 (d, Ar-*H*), 8.89 (s, pyrimidine-*H*), ^{13}C. NMR: 21.29 (*C*H$_3$), 22.23, 22.32, 22.70 (3*C*H$_3$),40.13(*C*-thiopyran-4), 43.56 (2C, HN(*C*H$_2$)$_2$), 45.11 (2C, N(*C*H$_2$)$_2$), 46.04 (N*C*H$_3$), 61.39 (*C*-5'), 66.19 (*C*-3'), 66.82 (*C*-2'), 67.35 (*C*-4'), 85.61 (*C*-1'), 121.1 - 147.6 (15*C*-*Ar*), 167.5 (*C*O), 169.5, 170.3, 173.1 (3*C*O), Its MS (m/z), 694 (M^+, 19%), $C_{34}H_{38}N_4O_{10}S$ (694.7).

***N*-(2',3',5'-*tri*-*O*-*acetyl*-*β*-*D*-*arabinofuranosyl*)-7-*methyl*-5-(4-*morpholin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thiochro meno*[2,3-d]*pyrimidine*-4-*one*-10,10-*dioxide* (7*c*).** It was obtained from compound **6f** and 2,3,5-tri-*O*-acetyl-*α*-*D*-arabinofuranosyl)-bromide (**11**), as yellow powder, m. p. 261˚C - 263˚C, IR (cm^{-1}, *v*), 1728 (3CO), 1672 (CO), 1335 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 1.93, 1.99, 2.11 (3s, 3C*H*$_3$CO), 2.23 (s, C*H*$_3$), 2.54 (m, 4H, N(C*H*$_2$)$_2$), 3.61 (m, 4H, O(C*H*$_2$)$_2$), 4.13 (m, *H*-4'), 4.18 (m, *H*-5', *H*-5''), 4.51 (s, thiopyran-*H*), 5.31 (m, *H*-3'), 5.39 (m, *H*-2'), 6.81 (d, *J* = 3.72 Hz, *H*-1'), 7.03 (m,

Ar-*H*), 7.09 (m, Ar-*H*), 7.15 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.27 (d, 2H, Ar-*H*), 8.00 (d, 2H, Ar-*H*), 8.80 (s, pyrimidine-*H*), ^{13}C.NMR: 21.90 (*C*H$_3$), 22.21, 22.30, 22.57 (3*C*H$_3$), 41.32 (*C*-thiopyran-4), 45.76 (2C, N(*C*H$_2$)$_2$), 60.98 (*C*-5'), 63.28 (2C, O(*C*H$_2$)$_2$), 66.30 (*C*-3'), 66.87 (*C*-2'), 67.41 (*C*-4'), 86.03 (*C*-1'), 119.8 - 148.3 (15*C*-*Ar*), 166.8 (*C*O), 170.1, 171.3, 172.9 (3*C*O), Its MS (m/z), 681 (M$^+$, 21%), $C_{33}H_{35}N_3O_{11}S$ (681.7).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thio chromeno*[2,3-d]*pyrimidine*-4-*one*-10,10-*dioxide* (8*a*).** It was obtained from compound **6d** and 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl)-bromide (**12a**), as a pale yellow powder, m. p. 192˚C - 194˚C, IR (cm^{-1}, *v*), 3285 (br, NH), 1725(4CO), 1680(CO), 1345(CS), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 1.94, 2.02, 2.11, 2.14 (4s, 12H, 4C*H*$_3$CO), 2.28 (s, C*H*$_3$), 2.53 (m, 4H, N(C*H*$_2$)$_2$), 3.05 (m, 4H, HN(C*H*$_2$)$_2$), 3.98 (m, *H*-5'), 4.25 (m, *H*-6', *H*-6''), 4.36 (m, *H*-4'), 4.39 (s, thiopyran-*H*), 5.01 (t, *H*-2'), 5.19 (t, 1H, *J* = 9.60 Hz, *H*-3'), 5.95 (d, *J* =10.67 Hz, *H*-1'), 7.01 (m, Ar-*H*), 7.08 (m, Ar-*H*), 7.17 (s, Ar-*H*), 7.21 (m, Ar-*H*), 7.27 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.87 (s, pyrimidine-*H*), 10.17 (br, NH), ^{13}C. NMR: 21.67 (*C*H$_3$), 22.12, 22.23, 22.36, 22.55(4CH$_3$), 39.87(*C*-thiopyran-4), 43.7 (2C, HN(*C*H$_2$)$_2$), 46.3 (2C, N(*C*H$_2$)$_2$), 60.21 (C-6'), 65.23 (C-3'), 67.70 (C-2'), 69.35 (C-4'), 75.34 (C-5'), 87.19 (C-1'), 120.7-147.9 (15*C*-*Ar*), 166.9 (*C*O), 169.3, 170.2, 171.3, 171.9 (4CO), Its MS (m/z), 752 (M$^+$, 32%), $C_{36}H_{40}N_4O_{12}S$ (752.7).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-[4-(4-*methyl*-*piperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (8*b*).** It was obtained from compound **6e** and 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl)-bromide (**12a**), as a pale yellow powder, m. p. 207˚C - 209˚C, IR (cm^{-1}, *v*), 1728 (CO),1667(CO),1342(SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 1.92, 1.99, 2.02, 2.11 (4s, 12H, 4C*H*$_3$CO), 2.26 (s, C*H*$_3$), 2.46 (s, C*H*$_3$), 2.58 (m, N(C*H*$_2$)$_2$), 2.69 (m, N(C*H*$_2$)$_2$), 3.83 (m, *H*-5'), 4.11 (m, *H*-6', *H*-6''), 4.28 (m, *H*-4'), 4.46 (s, thiopyran-*H*), 4.89 (t, *H*-2'), 5.45 (t, *J* = 9.60 Hz, *H*-3'), 5.96 (d, *J* = 10.54 Hz, *H*-1'), 7.01 (m, Ar-*H*), 7.08 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.26 (d, 2H, Ar-*H*), 7.95 (d, 2H, Ar-*H*), 8.84 (s, pyrimidine-*H*), Its MS (m/z), 766 (M$^+$, 31%), $C_{37}H_{42}N_4O_{12}S$ (766.8).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-(4-*morpholin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (8*c*).** It was obtained from compound **6f** and 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-glucopyranosyl)-bromide (**12a**), as yellow powder, m. p. 258˚C - 260˚C, IR (cm^{-1}, *v*), 1728 (CO), 1678 (CO), 1341 (SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 1.98, 2.04, 2.15, 2.19 (4s, 12H, 4C*H*$_3$CO), 2.24 (s, C*H*$_3$), 2.56 (m, 4H, N(C*H*$_2$)$_2$), 3.63 (m, 4H, O(C*H*$_2$)$_2$), 4.01 (m, *H*-5'), 4.22 (m, *H*-6', *H*-6''), 4.36 (m, *H*-4'), 4.51 (s, thiopyran-*H*), 4.87 (t, *H*-2'), 5.21 (t, *J* = 9.61 Hz, *H*-3'), 6.03 (d, *J* = 10.70 Hz, *H*-1'),7.01 (m, Ar-*H*),7.07 (m, Ar-*H*), 7.11 (s, Ar-*H*), 7.18 (m, Ar-*H*), 7.23 (d, Ar-*H*), 7.98 (d, Ar-*H*), 8.90 (s, pyrimidine-*H*), ^{13}C.NMR: 21.89 (*C*H$_3$), 22.17, 22.25, 22.38, 22.63(4CH$_3$), 43.26 (*C*-thiopyran-4), 45.91(2C,N(*C*H$_2$)$_2$), 64.92(2C,O(*C*H$_2$)$_2$), 121.9 - 147.6(15*C*-*Ar*), 165.9(CO), 169.3, 170.2, 171.3, 171.9 (4CO), Its MS(m/z), 753(M$^+$, 25%), $C_{36}H_{39}N_3O_{13}S$ (753.7).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thio chromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (8*d*).** It was obtained from compound **6d** and 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-galactopyranosyl)-bromide (**12b**), as a pale yellow powder, m. p. 178˚C - 180˚C, IR (cm^{-1}, *v*), 3274 (br, NH), 1730(4CO), 1676 (CO)1345 (CS), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 1.97, 2.05, 2.13, 2.16(4s, 12H, 4C*H*$_3$CO), 2.25 (s, C*H*$_3$), 2.55 (m, 4H, N(C*H*$_2$)$_2$), 3.02 (m, 4H, HN(C*H*$_2$)$_2$), 3.96 (m, *H*-5'), 4.23 (m, *H*-6', *H*-6''), 4.38 (m, *H*-4'), 4.41 (s, thiopyran-*H*), 5.13 (t, 1H, *H*-2'), 5.20 (t, *J* = 9.78 Hz, *H*-3'), 6.01 (d, *J* = 10.64 Hz, *H*-1'), 7.03 (m, Ar-*H*), 7.11 (m, Ar-*H*), 7.19 (s, Ar-*H*), 7.23 (m, Ar-*H*), 7.31 (d, Ar-*H*), 8.00 (d, Ar-*H*), 8.90 (s, pyrimidine-*H*), 10.25 (br, NH), ^{13}C.NMR:21.88(*C*H$_3$), 22.17, 22.26, 22.38, 22.59 (4CH$_3$), 40.56(*C*-thiopyran-4), 43.8 (2C, HN(*C*H$_2$)$_2$), 46.7 (2C, N(*C*H$_2$)$_2$), 60.56 (C-6'), 65.78 (C-3'), 67.78 (C-2'), 70.13 (C-4'), 74.64 (C-5'), 87.21 (C-1'), 121.4 - 147.6 (15*C*-*Ar*), 167.2 (*C*O), 170.1, 170.7, 171.8, 172.4 (4*C*O), Its MS (m/z), 752(M$^+$, 41%), $C_{36}H_{40}N_4O_{12}S$ (752.7).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-[4-(4-*methyl*-*piperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (8*e*).** It was obtained from compound **6e** and 2,3, 4,6-tetra-*O*-acetyl-*α*-*D*-galacto-pyranosyl)-bromide (**12b**), as yellow powder, m. p. 219˚C - 221˚C, IR (cm^{-1}, *v*), 1723 (CO),1673(CO), 1340(SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 1.94, 2.02, 2.12, 2.19 (4s, 12H,4C*H*$_3$CO), 2.29 (s, C*H*$_3$), 2.45 (s, C*H*$_3$), 2.53(m, N(C*H*$_2$)$_2$), 2.70 (m, N(C*H*$_2$)$_2$), 3.92 (m, 1H, *H*-5'), 4.07 (m, 2H, *H*-6', *H*-6''), 4.19(m, *H*-4'), 4.52 (s, thiopyran-*H*), 4.87 (t, *H*-2'), 5.29 (t, 1H, *J* = 9.78 Hz, *H*-3'), 5.99 (d, *J* = 10.64 Hz, *H*-1'), 7.00(m, Ar-*H*), 7.07(m, H, Ar-*H*), 7.12 (s, Ar-*H*), 7.21 (m, Ar-*H*), 7.28 (d, Ar-*H*), 7.98 (d, Ar-*H*), 8.87 (s, pyrimidine-*H*), Its MS (m/z), 766 (M$^+$, 31%), $C_{37}H_{42}N_4O_{12}S$ (766.8).

***N*-(2',3',4',6'-*tetra*-*O*-*acetyl*-*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-(4-*morpholin*-1-*yl*-*phenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (8*f*).** It was obtained from compound **6f** and 2,3,4,6-tetra-*O*-acetyl-*α*-*D*-galactopyranosyl)-bromide (**12b**), as yellow powder, m. p. 239˚C - 241˚C, IR (cm^{-1}, *v*), 1727 (CO), 1672 (CO), 1341(SO), ^{1}H.NMR (DMSO-d_6, *δ*,

ppm): 1.96, 2.03, 2.07, 2.13 (4s, 12H, 4CH_3CO), 2.25 (s, CH_3), 2.56 (m, 4H, N(CH_2)$_2$), 3.63 (m, 4H, O(CH_2)$_2$), 3.92 (m, *H*-5'), 4.07 (m, 2H, *H*-6', *H*-6''), 4.19 (m, *H*-4'), 4.53 (s, thiopyran-*H*), 4.87 (t, *H*-2'), 5.29 (t, *J* = 9.64 Hz, *H*-3'), 5.99 (d, *J* = 10.60 Hz, *H*-1'), 6.98 (m, Ar-*H*), 7.06 (m, Ar-*H*), 7.11 (s, Ar-*H*), 7.15 (m, Ar-*H*), 7.21 (d, 2H, Ar-*H*), 8.00 (d, 2H, Ar-*H*), 8.89 (s, pyrimidine-*H*), ^{13}C. NMR: 22.67 (*C*H_3), 43.31(*C*-thiopyran-4), 45.87 (2C, N(*C*H_2)$_2$), 60.39 (C-6'), 63.76 (2C, O(*C*H_2)$_2$), 66.73 (C-3'), 67.84 (C-2'), 70.16 (C-4'), 74.71 (C-5'), 87.23 (C-1'), 120.8-148.9 (15*C*-*Ar*), 166.6 (*C*O), 169.8, 170.2, 171.8, 172.7 (4*C*O), Its MS (m/z), 753 (M^+, 23%), $C_{36}H_{39}N_3O_{13}S$ (753.7).

Synthesis of diacetylated N-(*β*-D-glycosidylthio)-3, 5-dihydro-4H-thiochromeno[2,3-*d*]pyrimidine-4-one-10,10-dioxide (9a-c) and (10a-f). ***General procedure*:** Acetylated compound **7a-c** or **8a-f** (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. Purification by heating the crude in n-hexane (100 ml, three times) provided **9a-c** or **10a-f** as yellow solid. Crystallization from methanol gave a pale yellow powder.

***N*-(*β*-*D*-*arabinofuranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*ylphenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*] *pyrimidine*-4-*one*-10,10-*dioxide* (9*a*)**.** It was obtained from **7a**, as white powder, m. p. 239 C - 241˚C, IR (cm^{-1}, *v*), 3500 (brs, OH), 3280 (br, NH),1676(CO),1330 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.24 (s, CH_3), 2.51 (m, 4H, N(CH_2)$_2$), 3.00 (m, 4H, HN(CH_2)$_2$), 3.80 (m, *H*-5', *H*-5''), 4.12 (m, *H*-4'), 4.50 (s, thiopyran-*H*), 4.80 (t, *H*-2'), 5.14 (t, *J* = 5.41 Hz, *J* = 4.97 Hz, OH-C(5'), 5.22 (d, *J* = 4.46 Hz, OH-C(3'), 5.41 (d, *J* = 5.95 Hz, OH-C(2'), 5.66 (t, *J* = 9.80 Hz, *H*-3'), 6.88 (d, *J* = 5.63 Hz, *H*-1'), 7.03 (m, Ar-*H*), 7.10 (m, Ar-*H*), 7.16 (s, Ar-*H*), 7.23 (m, Ar-*H*), 7.28 (d, 2H, Ar-*H*), 8.07 (d, 2H, Ar-*H*), 8.78 (s, pyrimidine-*H*), 10.55 (br, NH), ^{13}C.NMR: 22.03 (*C*H_3), 40.13 (*C*-thiopyran-4), 43.53 (2C, HN(*C*H_2)$_2$), 46.02 (2C, N(*C*H_2)$_2$), 60.86 (*C*-5'), 65.33 (*C*-3'), 67.58 (*C*-2'), 69.26 (*C*-4'), 87.71 (*C*-1'), 120.6 - 147.9 (15*C*- *Ar*), 166.7 (*C*O), Its MS (m/z), 554 (M^+, 31%), $C_{27}H_{30}N_4O_7S$ (554.6).

***N*-(*β*-*D*-*arabinofuranosyl*)-7-*methyl*-5-[4-(4-*methyl*-*pip erazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno* [2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (9*b*)**.** It was obtained from compound **7b**, as pale yellow powder, m. p. 271˚C - 273˚C, IR (cm^{-1}, *v*), 3480 (brs, OH), 1682 (CO), 1354 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.21 (s, CH_3), 2.27 (s, CH_3), 2.56 (m, 4H,N(CH_2)$_2$),3.09 (m, 4H, HN(CH_2)$_2$), 3.78 (m, *H*-5', *H*-5''), 4.13 (m, *H*-4'), 4.50 (s, thiopyran-*H*), 4.69 (t, *H*-2'), 5.12 (t, *J* = 5.41 Hz, *J* = 4.94 Hz, OH-C(5'), 5.22 (d, *J* = 4.45 Hz, OH-C(3'), 5.35 (d, *J* = 5.95 Hz, OH-C(2'), 5.70 (t, *J* = 9.58 Hz, *H*-3'), 6.91 (d, *J* = 5.69 Hz, *H*-1'), 7.01 (m, Ar-*H*), 7.09 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.20 (m, Ar-*H*), 7.26 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.69 (s, pyrimidine-*H*), ^{13}C.NMR: 21.35(*C*H_3), 40.17(*C*-thio-pyran-4), 43.56(2C, HN(*C*H_2)$_2$), 45.11(2C, N(*C*H_2)$_2$, 46.04 (N*C*H_3), 61.41 (*C*-5'), 66.21 (*C*-3'), 66.84 (*C*-2'), 67.39 (*C*-4'), 85.70 (*C*-1'), 120.7 - 147.9 (15*C*-*Ar*), 166.8 (*C*O), Its MS (m/z), 568(M^+, 28%), $C_{28}H_{32}N_4O_7S$ (568.6).

***N*-(*β*-*D*-*arabinofuranosyl*)-7-*methyl*-5-(4-*morpholin*-1-*yl*)*phenyl*-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*] *pyrimidine*-4-*one*-10,10-*dioxide* (9*c*)**.** It obtained from **7c,** as yellow powder, m. p. 289˚C - 291˚C, IR (cm^{-1}, *v*), 3460 (brs, OH), 1677 (CO), 1334 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.25 (s, CH_3), 2.48 (m, 4H, N(CH_2)$_2$), 3.59 (m, 4H, O(CH_2)$_2$), 3.83 (m, *H*-5', *H*-5''), 4.09 (m, *H*-4'), 4.49 (s, thiopyran-*H*), 4.63 (t, *H*-2'), 5.07 (t, *J* = 5.40 Hz, *J* = 4.94 Hz, OH-C(5'), 5.21 (d, *J* = 4.41 Hz, OH-C(3'), 5.34 (d, *J* = 5.95 Hz, OH-C(2'), 5.67(t, *J* = 9.56 Hz, *H*-3'), 6.88 (d, *J* = 5.67 Hz, *H*-1'), 7.05 (m, Ar-*H*), 7.11 (m, Ar-*H*), 7.17 (s, Ar-*H*), 7.21 (m, Ar-*H*), 7.28 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.92 (s, pyrimidine-*H*), ^{13}C.NMR: 22.07 (*C*H_3), 41.26 (*C*-thiopyran-4), 46.06 (2C, N(*C*H_2)$_2$), 61.08 (*C*-5'), 63.45 (2C, O(*C*H_2)$_2$), 66.41 (*C*-3'), 66.65 (*C*-2'), 67.70 (*C*-4'), 85.73 (*C*-1'), 121.8 - 148.5 (15*C*-*Ar*), 166.9 (*C*O), Its MS (m/z), 555 (M^+, 29%), $C_{27}H_{29}N_3O_8S$ (555.6).

***N*-(*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*yl* -*phenyl*)-3,5-*dihydro*-4*H*-*thio*-*chromeno*[2,3-*d*] *pyrimidine*-4-*one*-10,10-*dioxide* (10a)**.** It obtained from **8a**, as a white powder, m. p. 234˚C - 236˚C, IR (cm^{-1}, *v*), 3490 (brs, OH), 3250 (br, NH),1668 (CO), 1345 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.23 (s, CH_3), 2.50 (m, 4H, N(CH_2)$_2$), 3.01 (m, 4H, HN(CH_2)$_2$), 4.35 (s, thiopyran-*H*), 3.87 (m, *H*-5'), 4.11 (m, *H*-6', *H*-6''), 4.27 (m, *H*-4'), 4.60 (br, D_2O-exchangeable *OH*), 4.85 (t, *H*-2'), 5.04 (br, D_2O-exchangeable *OH*), 5.13 (t, *J* = 9.61 Hz, *H*-3'), 5.18 (d, *J* = 4.83 Hz, D_2O-exchangeable *OH*), 5.57 (br, D_2O-exchangeable *OH*), 6.04 (d, *J* = 10.61 Hz, *H*-1'), 7.00 (m, Ar-*H*), 7.05 (m, Ar-*H*), 7.15 (s, Ar-*H*), 7.22 (m, Ar-*H*), 7.29 (d, Ar-*H*), 8.02 (d, Ar-*H*), 8.90 (s, pyrimidine-*H*), 10.28 (br, NH), ^{13}C.NMR: 21.59 (*C*H_3), 39.79 (*C*-thiopyran-4), 43.82 (2C, HN(*C*H_2)$_2$), 46.32 (2C, N(*C*H_2)$_2$), 61.56 (C-6'), 66.37 (C-3'), 68.40 (C-2'), 68.97 (C-4'), 77.79 (C-5'), 89.63 (C-1'), 120.5 - 148.2 (15*C*-*Ar*), 166.9 (*C*O), Its MS (m/z), 584 (M^+, 26%), $C_{28}H_{32}N_4O_8S$ (584.6).

***N*-(*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-[4-(4-*methyl* *piperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno*[2, 3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (10*b*)**.** It obtained from **8b**, as a pale yellow powder, m. p. 243˚C - 245˚C, IR (cm^{-1}, *v*), 3480 (brs, OH), 1677(CO), 1339 (SO), ^{1}H.NMR (DMSO-d_6, δ, ppm): 2.28 (s, CH_3), 2.44 (s, CH_3), 2.56 (m, N(CH_2)$_2$), 2.70 (m, N(CH_2)$_2$), 3.81 (m, *H*-5'), 4.01 (m, *H*-6', *H*-6''), 4.31 (m, *H*-4'), 4.41 (s,

thiopyran-*H*), 4.54 (br, D_2O-exchangeable *OH*), 4.79 (t, *H*-2'), 5.03 (br, D_2O-exchangeable-*OH*), 5.12 (t, *J* = 9.64 Hz, *H*-3'), 5.19 (d, *J* = 5.0 Hz, D_2O-exchangeable *OH*), 5.60 (br,D_2O-exchange-able *OH*), 6.07 (d, *J* = 10.54 Hz, *H*-1'), 7.00 (m, Ar-*H*), 7.06 (m, Ar-*H*), 7.11(s, Ar-*H*), 7.16 (m, Ar-*H*), 7.21 (d, Ar-*H*), 7.92 (d, Ar-*H*), 8.93 (s, pyrimidine-*H*), Its MS (m/z), 598 (M^+, 27%), $C_{29}H_{34}N_4O_8S$ (598.6).

***N*-(*β*-*D*-*glucopyranosyl*)-7-*methyl*-5-(4-*morpholin*-1-*yl*) *phenyl*-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-d]*pyrimi dine*-4-*one*-10,10-*dioxide* (10*c*).** It obtained from **8c**, as yellow powder, m. p. 289˚C - 291˚C, IR (cm^{-1}, *v*), 3470 (brs, OH), 1675 (CO), 1345 (SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.29 (s, CH_3), 2.53 (m, 4H, N(CH_2)$_2$), 3.67 (m, 4H, O(CH_2)$_2$), 3.92 (m, *H*-5'), 4.06 (m, *H*-6', *H*-6''), 4.35 (m, *H*-4'), 4.56 (s, thiopyran-*H*), 4.97 (t, *H*-2'), 4.64 (br, D_2O-exchangeable *OH*), 5.06 (br, D_2O-exchangeable *OH*), 5.11 (d, *J* = 4.82 Hz, D_2O-exchang-eable *OH*), 5.16 (t, *J* = 9.55 Hz, *H*-3'), 5.61 (br, D_2O-exchangeable *OH*), 6.13 (d, *J* = 10.61 Hz, *H*-1'), 7.03 (m, Ar-*H*), 7.09 (m, Ar-*H*), 7.15 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.24 (d, 2H, Ar-*H*), 8.01 (d, 2H, Ar-*H*), 8.83 (s, pyrimidine-*H*), ^{13}C.NMR: 21.89 (*C*H_3), 43.26 (*C*-thiopyran-4), 45.91 (2C, N(*C*H_2)$_2$), 61.45 (C-6'), 64.81 (2C, O(*C*H_2)$_2$), 66.40 (C-3'), 67.89 (C-2'), 68.95 (C-4'), 77.82 (C-5'), 89.71 (C-1'), 120.8 - 148.4 (15*C*-*Ar*), 165.9 (CO), Its MS (m/z), 585 (M^+, 30%), $C_{28}H_{31}N_3O_9S$ (585.6)

***N*-(*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-(4-*piperazin*-1-*ylphenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*] *pyrimidine*-4-*one*-10,10-*dioxide* (10*d*).** It obtained from **8d**, as a white powder, m. p. 229˚C - 231˚C, IR (cm^{-1}, *v*), 3530 (br, OH), 3315 (br, NH), 1675 (CO), 1339 (SO), ^{1}H.NMR (DMS-O-d_6, *δ*, ppm): 2.31 (s, CH_3), 2.52 (m, 4H, N(CH_2)$_2$), 3.07 (m, 4H, HN(CH_2)$_2$), 3.85 (m, *H*-5'), 4.13 (m, *H*-6', *H*-6''), 4.29 (m, *H*-4'), 4.37 (s, thiopyran-*H*), 4.57 (br, D_2O-ex-changeable *OH*), 4.87 (t, *H*-2'), 5.08 (br, D_2O- exchangeable *OH*), 5.15 (t, *J* = 9.70 Hz, *H*-3'), 5.20 (d, *J* = 4.84 Hz D_2O-exchangeable-*OH*), 5.59 (br, D_2O-exchange able *OH*), 6.07 (d, *J* = 10.65 Hz, *H*-1'), 7.02 (m, Ar-*H*), 7.09 (m, Ar-*H*), 7.17 (s, Ar-*H*), 7.23 (m, Ar-*H*), 7.31 (d, Ar-*H*), 8.05 (d, Ar-*H*), 8.86 (s, pyrimidine-*H*), 10.45 (br, NH), ^{13}C. NMR: 21.45 (*C*H_3), 40.19 (*C*- thiopyran-4), 43.74 (2C, HN(*C*H_2)$_2$), 46.29 (2C, N(*C*H_2)$_2$), 61.70 (C-6'), 66.41 (C-3'), 68.39 (C-2'), 69.07 (C-4'), 78.29 (C-5'), 89.87 (C-1'), 120.7 - 148.9 (15*C*-*Ar*), 167.5 (*C*O), Its MS (m/z), 584 (M^+, 34%), $C_{28}H_{32}N_4O_8S$ (584.6).

***N*-(*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-[4-(4-*methyl piperazin*-1-*yl*)*phenyl*]-3,5-*dihydro*-4*H*-*thiochromeno* [2,3-*d*]*pyrimidine*-4-*one*-10,10-*dioxide* (10*e*).** It obtained from **8e**, m. p. 271˚C - 273˚C, IR (cm^{-1}, *v*), 3485 (brs, OH), 1668 (CO), 1341 (SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.23 (s, CH_3), 2.47 (s, CH_3), 2.53 (m, N(CH_2)$_2$), 2.69 (m, N(CH_2)$_2$), 3.78 (m, 1H, *H*-5'), 4.03 (m, *H*-6', *H*-6''), 4.33 (m, *H*-4'), 4.51 (s, thiopyran-*H*), 4.56 (br, D_2O-exchangeable *OH*), 4.81 (t, *H*-2'), 5.11 (br, D_2O-exchangeable *OH*), 5.15 (t, *J* = 9.70 Hz, *H*-3'), 5.21 (d, *J* = 5.0 Hz, D_2O-exchangeable *OH*), 5.63 (br, D_2O-exchangeable *OH*), 6.08 (d, *J* = 10.59 Hz, *H*-1'), 7.01 (m, Ar-*H*), 7.09 (m, Ar-*H*), 7.13 (s, Ar-*H*), 7.19 (m, Ar-*H*), 7.23 (d, Ar-*H*), 7.98 (d, Ar-*H*), 8.83 (s, pyrimidine-*H*), Its MS(m/z),598(M^+, 27%),$C_{29}H_{34}N_4O_8S$ (598.6).

***N*-(*β*-*D*-*galactopyranosyl*)-7-*methyl*-5-(4-*morpholin*-1 -*ylphenyl*)-3,5-*dihydro*-4*H*-*thiochromeno*[2,3-*d*] *pyrimidine*-4-*one*-10,10-*dioxide* (10*f*).** It obtained from **8f**, as pale brown powder, m. p. 267˚C - 269˚C, IR (cm^{-1}, *v*), 3495 (brs, OH), 1668 (CO), 1350 (SO), ^{1}H.NMR (DMSO-d_6, *δ*, ppm): 2.25 (s, CH_3), 2.50 (m, 4H, N(CH_2)$_2$), 3.65 (m, 4H, O(CH_2)$_2$), 3.96 (m, *H*-5'), 4.05 (m, *H*-6', *H*-6''), 4.41 (m, *H*-4'), 4.60 (s, thiopyran-*H*), 4.98 (t, *H*-2'), 4.70 (br, D_2O-exchangeable *OH*), 5.10 (br, D_2O-exchangeable *OH*), 5.16 (d, *J* = 4.81 Hz, D_2O-exchangeable *OH*), 5.19 (t, *J* = 9.64 Hz, *H*-3'), 5.63 (br, D_2O-exchangeable *OH*), 6.15 (d, *J* = 10.65 Hz, *H*-1'), 6.98 (m, Ar-*H*), 7.04 (m, Ar-*H*), 7.12 (s, Ar-*H*), 7.20 (m, 1H, Ar-*H*), 7.25 (d, 2H, Ar-*H*), 8.03 (d, 2H, Ar-*H*), 8.87 (s, pyrimidine-*H*), ^{13}C. NMR: 21.97 (*C*H_3), 42.69 (*C*-thiopyran-4), 45.65 (2C, N(*C*H_2)$_2$), 61.38 (C-6'), 64.69 (2C, O(*C*H_2)$_2$), 66.35 (C-3'), 67.91 (C-2'), 68.93 (C-4'), 77.85 (C-5'), 89.76 (C-1'), 121.5-148.7 (15*C*-*Ar*), 166.4 (CO), Its MS (m/z), 585 (M^+, 30%), $C_{28}H_{31}N_3O_9S$ (585.6).

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