A novel α-haloacid based clay-catalysed expeditious synthesis of pyrazoloimidazole-2-thione-*N*-nucleosides

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Abstract : An expeditious mineral (Montmorillonite K-10 clay) catalysed cyclo-condensation of chloroacetic acid with arylthiourea followed by Knoevenagel condensation with aromatic aldehyde in presence of sodium acetate under solvent-free microwave irradiation yields 3-aryl-5-benzylideno-2-thiohydantoins **4(a-l)**. Compounds **4 (a-l)** with hydrazine hydrate in glacial acetic acid furnishe the intermediate acetyl hydrazone of **4(a-l)** which on cycloisomerisation under reaction conditions give 1,8-diaryl-4,8-dihydro-1-acetylpyrazolo[3,4-c]imidazol-2-thiones **5(a-l)**. On glycosylation with 1,2,3,5-tetra-*O*-acetyl-β-D-furanose in presence *p*-toluene sulfonic acid under microwave irradiation followed by deacetylation with NaOMe / MeOH compounds **5 (a-l)** yields, 1,8-diaryl-3(β-D-ribofuranosyl)-4,8-dihydro-1-acetyl[3,4-c]imidazol-2-thione **6(a-l)**.

Keywords: Pyrazoloimidazol-2-thione*N*-nucleoside, montmorillonite K-10 clay supported, Knoevenagel condensation ,solvent-free, microwave-irradiation, glycosylation , Green chemistry ,.

Introduction: Compounds with imidazole scaffolds have recently received attention because of their pharmacological properties.[1-3] Most important of these are 2-thioxo-imidazolidinones which exhibit antiviral particularly anti HIV activity.[4-5] Most available drugs approved by FDA for the treatment of AIDS include nucleoside analogues and protease inhibitor but no attempt has been made so far to synthesize nucleoside analogues incorporating 2-thioxoimidazolidinones as nucleobase although they appear to be attractive structural class for exploiting chemical diversity and generating a drug like library to screen for lead candidates. Similarly pyrazole moiety containing compounds gained importance in recent years due to their antiviral, antibacterial and other interesting biological effects.[6] The study on the influence of structure on activity have shown that by fusing one heterocyclic moiety with other, most of the time the pharmacological profile was enhanced many folds than any one of the heterocyclic moiety.[7] The fight against HIV by developing more efficacious multi-target drugs has been the driving force for fusing pyrazole moiety with and glycosylation of 2-thioxoimidazolidinones.

The application of molecular diversity technique to drug discovery is a multidisciplinary effort ranging from computational chemistry to engineering to organic synthesis to molecular biology. The main objective of the work described here is to provide an account of one aspect of molecular diversity based drug

discovery *viz.* the development of general synthetic strategy for generation of nucleoside analogues for screening of lead molecules for novel assays in the archives a chemicals amassed through organic synthesis.[8]

With increasing global environmental concerns application of eco-friendly and mineral supported reagents, solvent-free reactions and microwave irradiation techniques[9-12] has increased dramatically in recent years since by doing so use of expensive and hazardous organic solvents and reagents can be avoided significantly.[13-16] Use of mineral supported reagents assisted by microwave irradiation under solvent-free conditions provide environmentally benign protocol with additional advantages such as enhanced reaction rate, higher yields of pure product, easier workup, better selectivity, improved ease of manipulation, rapid optimization of reactions in parallel which fulfill basic principles of green chemistry.

Encouraged by above reports and as part of our research programme for development of eco-friendly synthetic protocol for biologically active compounds[17-21] as well as in pursuing of our work on new solvent-free cyclisation process we developed a regioselective, novel, montmorillonite K-10 clay catalysed, microwave activated synthesis of hitherto unknown pyrazoloimidazol-2-thione *N*-nucleosides **(Scheme 1)**. Interestingly it is the first example of microwave induced synthesis of pyrazoloimidazol-2-thione *N*-nucleosides. The key element in our approach is the utilization of α-haloacid as a bifunctional building block whose application to the construction of various heterocycles of chemical and biological interest is well documented.[22-23]

Results &Discussion: An expeditious mineral (montomorillonite K-10clay) catalysed cyclocondensation of arylthiourea **1** with chloroacetic acid **2** under solvent-free microwave irradiation regioselectively gave 3-aryl-2-thioxoimidazolidin-4-one **(Scheme 2)** which on Knoevenagel condensation with aromatic aldehyde **3** in presence of CH_3COONa furnished 3-aryl-5-benzylideno-2-thiohydantoins 4a-l **(Scheme 1)** with 80-88% yields **(Table I)**. Regioselectivity obtained in cyclocondensation of arylyhiourea with chloroacetic acid was due to difference in nucleophilicity of $–NH_2$ and –NHAr groups. Additional delocalisation of electrons on aromatic ring in –NHAr makes it a poor nucleophile and hence $–NH_2$ group by nucleophilic substitution of α-halogen of $ClCH_2COOH$ resulted an intermediate which cyclised to produce **4 a-l (Scheme 2)**. Structure of **4 a-l** was supported by IR and ^1H NMR spectral analysis. Absorption bands in the region of 3300-3350 cm^{-1} for N-H, 3050 cm^{-1} for aromatic C-H, 1690 cm^{-1} for C=O, 1620 cm^{-1} for C=C, 1600, 1500, 1468 cm^{-1} for aromatic C-C, 1200 cm^{-1} for C=S and 1180 cm^{-1} for C-N stretching in IR spectra and signals at δ 7.2 - 7.4 as multiplet for aromatic protons, δ 4.80 as singlet for vinylic proton of benzylideno group and δ 2.1 - 2.5 as singlet for –NH- proton in ^1H NMR spectra were indicative of the synthesis of compounds **4a-l**.

Other mineral supports *viz.* silica gel, neutral or basic alumina were far less effective resulting in either no reaction (in case of basic alumina) or relatively very low yields (15-30%) of **4** (in case of silica gel and neutral alumina). In order to compare the final temperature

was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiation and was found to be <88°C. The reactions were also carried out using a thermostated oil-bath at the same temperature (88°C) as for the MW activated method but for a longer period of time **(Table I).** It was found that MW method has improved the yields significantly. MW enhancement of yields and reduction in reaction time can be rationalized on the basis of the formation of dipolar activated complex **I** from uncharged reactants complex II from uncharged adduct in these reactions **(Scheme 2)** and greater stabilization of the more dipolar activated complex by dipole-dipole interaction with electric field of the microwaves as compared to the less polar adduct which may reduce the activation energy [$G^{\#}$] resulting in the rate enhancement.Compounds **4a-l** with $NH_2NH_2.H_2O$ in glacial acetic acid produced acetyl hydrazones which on cycloisomerisation under reaction conditions at room temperature gave 1,8-diaryl-4,8-dihydro-1-acetylpyrazolo[3,4-c]imidazol-2-thiones **5a-l (Scheme 1** and **2)** in 78-86% yields **(Table I).** Absorption peaks at 3300-3350 cm^{-1} (N-H), 3050 cm^{-1} (Aromatic C-H), 1690 cm^{-1} (C=O), 1640 cm^{-1} (C=N), 1600, 1500, 1468 cm^{-1} (Aromatic C-C), 1200 cm^{-1} (C=S), in IR spectra and doublet at δ 2.0 for –NH- with *J*= 2.5 Hz, singlet at δ 2.00-2.08 for $-COCH_3$, multiplet at δ 3.63 for H-4 and doublet at δ 5.1-5.6 with *J*= 3.2 Hz for H-8 and multiplet at δ 6.90-7.80 for aromatic protons supported the formation of **5 a-l**.

Microwave assisted and *p*-CH_3-$C_6H_4.SO_3H$ catalysed glycosylation of **5 a-l** with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose followed by deacetylation with NaOMe / MeOH yielded 1,8-diaryl-3-(β-D-ribofuranosyl)-4,8-dihydro-1-acetylpyrazolo[3,4-c]imidazol-2-thiones **6 a-l (Scheme 1 and 2)** in 75-88% yields **(Table I).** The structure of **6 a-l** were also confirmed by spectral and elemental analysis. Spectra of all the synthesised compounds showed close similarity with spectral pattern of fused pyrazole moiety with 2-thioxoimidazolidine ring as well as β-D-ribofuranose sugar residue.Singlet at δ 2.02 for -$COCH_3$ protons, doublets at δ 3.60-3.65 with *J*= 3.2 Hz and at δ 5.1-5.6 with *J*= 3.2 Hz due to H-4 and H-8 respectively and multiplets at δ 6.46-8.14 due to aromatic protons in ^{1}H NMR spectra of **6 a-l** showed the pyrazoloimidazol-2-thione nucleus. Multiplets in the region at δ 3.65-3.80 due to four sugar protons as well as doublets at δ 4.96 with *J*= 4.2 Hz due to anomeric proton and broad singlet at δ 2.00 exchangeable with D_2O due to three –OH group were indicative of β-D-ribofuranosyl moiety in **6 a-l**.

In ^{13}C NMR spectral analysis in the region δ 108-165 for aromatic carbons and at δ 165-175 for C=S and C=O carbons and at δ 61-178 for sugar carbons supported that all synthesized compound have pyrazoloimidazolidin-2-thione *N*-ribofuranosidic skeleton.

Experimental Section: Melting points were determined by open glass capillary method and are uncorrected. All chemicals used were reagent grade and were used as received. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The completion of reactions was monitored by TLC (Merk silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400°C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in $CDCl_3$

using TMS as an internal reference (chemical shift in δ, ppm). Mass spectra were recorded on JEOL SX-303 (FAB) mass spectrophotometer at 70ev. Elemental analyses were carried out using a Coleman automatic C,H,N analyser.

3-Aryl-5-benzylideno-2-thioxohydantoin (4 a-l)

Method A (Thermal): To a solution of arylthioureaa **1** (0.01 mol), chloroacetic acid **2** aromatic aldehyde **3** (0.01 mol) and CH_3COONa (0.001 mol) in DMF (50 mL) was added montomorillonite K-10 clay (0.50 g) with constant stirring and the reaction mixture was refluxed on thermostated oil-bath at 90 ^oC for the time specified in **Table I**. Progress of the reaction was monitored by TLC (Hexane: MeOH; 6:4 v/v). After completion of the reaction the reaction mixture was cooled and poured into water, filtered and the product was extracted with ethanol (3x50 mL). The extract was evaporated under reduced pressure to obtain the final product which was recrystallised from ethanol to get analytically pure compounds **(4a-l)**.

Method B (Microwave irradiation): Montomorillonite K-10 clay (0.50g) was added to a solution of arylthiourea **1** (0.01mol) chloroacetice acid **2** (0.01 mol) aromatic aldehyde **3** (0.01 mol) and CH_3COONa (0.001 mol) in DMF (10ml) with thorough mixing and the solvent was evaporated under reduced pressure. The contents were taken in 20 ml vial and subjected to microwave irradiation at 600 W for 2 min. The reaction mixture was then thoroughly mixed outside the microwave oven for 2 min and again irradiated for another 2 min. This irradiation-mixing cycle was repeated for the total irradiation time **Table I**. After completion of the reaction as indicated by TLC (Hexane : MeOH, 6:4 v/v) the product was extracted with ethanol (3x8 mL). The extract was filtered and filtrate was evaporated under reduced pressure to obtain the product. The final product was recrystallised from ethanol to obtain analytically pure compounds (**4a-l**).

1,8-Diaryl-4,8-dihydro-1-acetylpyrazolo[3,4-c]imidazol-2-thione (5a-l) : A mixture of **4a-l** (0.002 mol), hydrazine hydrate (0.2 mol), glacial acetic acid (1 mL) was stirred thoroughly at room temperature for 4-6 h. The solid product, thus separated was triturated with water to get compounds **5a-l** which were filtered and purified byrecrystallisation from aqueous ethanol.

1,8-Diaryl-3-(*β*-D-ribofuranosyl)-4,8-dihydro-1-acetylpyrazolo[3,4-c]imidazol-2-thiones (6a-l): *β*-D-ribofuranosyl-1,2,3,5-tetraacetate (0.001 mol), *p*-TsOH (0.03 g) and compound **5a-l** (0.001 mol) were mixed thoroughly and taken in 20 mL vial. The reaction mixture was subjected to microwave irradiation for 2 min and again irradiated for another 2 min. This irradiation-mixing cycle was repeated for the total irradiation time **(Table I)**. After completion of reaction as indicated by TLC, the resulting oil was dissolved in absolute MeOH (1.5 mL) and allowed to stand for 1 h at room temperature to get the crude product. It was filtered, recrystallised from absolute MeOH and dried in vacuum to get the crude product (acylated *N*-nucleoside).

The acylated *N*-nucleosides (0.0016 mol) in dry MeOH (20 mL) and 1 mL solution of MeONa (prepared by adding 0.1 g Na in 20 mL of dry MeOH) were taken in 100 mL stoppered flask and the reaction mixture was allowed to stand for 3-4 h with occasional shaking. The resulting solution on neutralization with dil. HCl

yielded nucleosides **6a-l** which were filtered and recrystallised from ethanol to get analytically pure samples.

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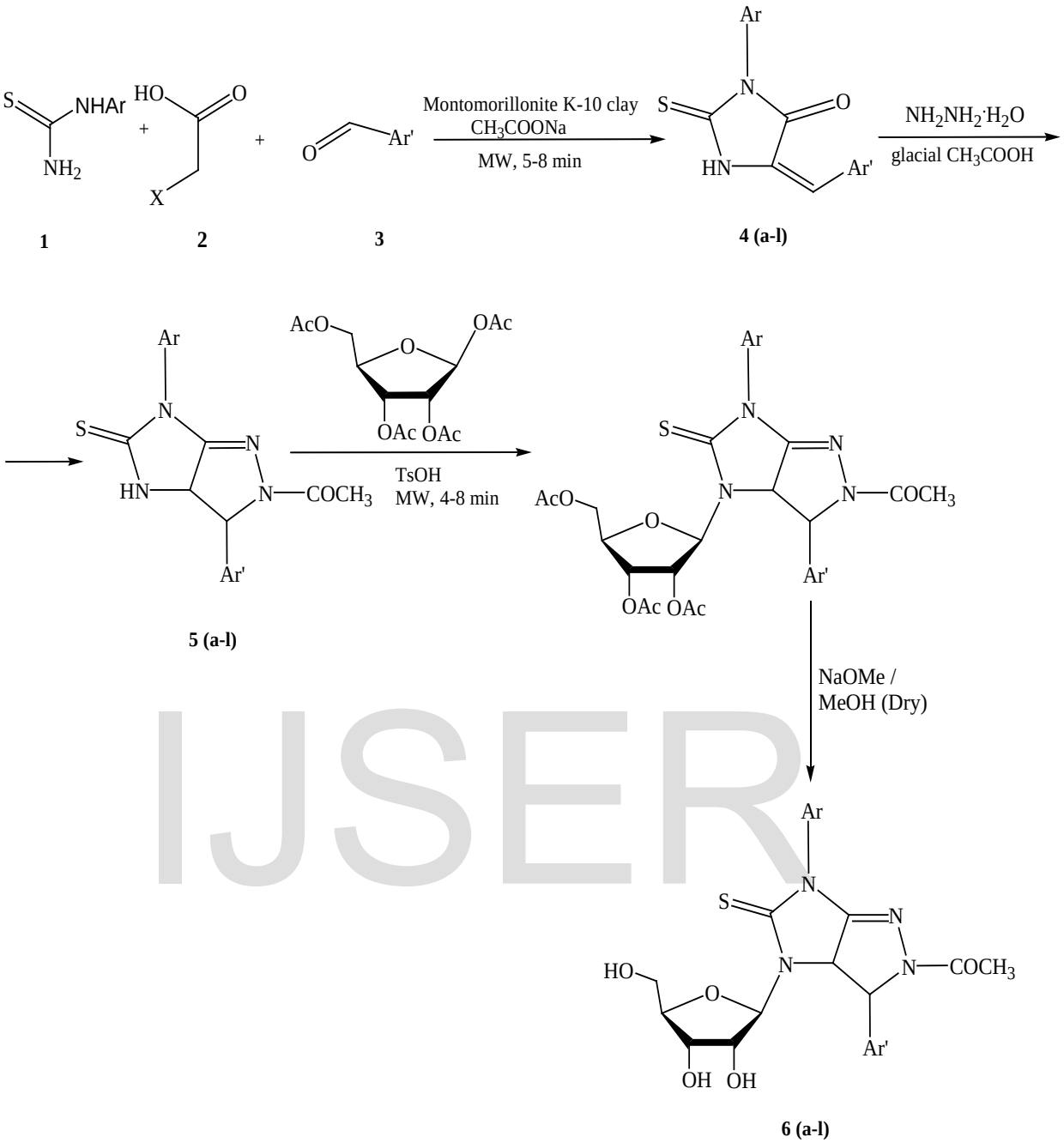

1 **2** **3** **4 (a-l)** **5 (a-l)** **6 (a-l)**

Scheme 1

Compd	Ar	Ar'	Compd	Ar	Ar'
4a	C_6H_5	C_6H_5	**5g**	4-Me- C_6H_4	C_6H_5
4b	C_6H_5	4-Cl-C_6H_4	**5h**	4-Me- C_6H_4	4-Cl-C_6H_4
4c	C_6H_5	4-HO-C_6H_4	**5i**	4-Me- C_6H_4	4-HO- C_6H_4
4d	C_6H_5	4-MeO- C_6H_4	**5j**	4-Me- C_6H_4	4-MeO- C_6H_4
4e	C_6H_5	2-NO_2- C_6H_4	**5k**	4-Me- C_6H_4	2-NO_2- C_6H_4
4f	C_6H_5	3-MeO, 4-HO-C_6H_3	**5l**	4-Me- C_6H_4	3-MeO, 4-HO-C_6H_3

4g	4-Me-C_6H_4	C_6H_5	**6a**	C_6H_5	C_6H_5
4h	4-Me-C_6H_4	4-Cl-C_6H_4	**6b**	C_6H_5	4-Cl-C_6H_4
4i	4-Me-C_6H_4	4-HO- C_6H_4	**6c**	C_6H_5	4-HO- C_6H_4
4j	4-Me-C_6H_4	4-MeO- C_6H_4	**6d**	C_6H_5	4-MeO- C_6H_4
4k	4-Me-C_6H_4	2-NO_2- C_6H_4	**6e**	C_6H_5	2-NO_2- C_6H_4
4l	4-Me-C_6H_4	3-MeO, 4-HO-C_6H_3	**6f**	C_6H_5	3-MeO, 4-HO-C_6H_3
5a	C_6H_5	C_6H_5	**6g**	4-Me- C_6H_4	C_6H_5
5b	C_6H_5	4-Cl-C_6H_4	**6h**	4-Me- C_6H_4	4-Cl-C_6H_4
5c	C_6H_5	4-HO- C_6H_4	**6i**	4-Me- C_6H_4	4-HO- C_6H_4
5d	C_6H_5	4-MeO- C_6H_4	**6j**	4-Me- C_6H_4	4-MeO- C_6H_4
5e	C_6H_5	2-NO_2- C_6H_4	**6k**	4-Me- C_6H_4	2-NO_2- C_6H_4
5f	C_6H_5	3-MeO, 4-HO-C_6H_3	**6l**	4-Me- C_6H_4	3-MeO, 4-HO-C_6H_3

Table 1: Physical and spectral data of compounds 4 a-l, 5 a-l and 6 a-l

Cmpd	Mol.Formula[a] (Mol. wt)	Time		Yield [b](%)		m.p. (°C)	IR (KBr, υ cm^{-1})	^{1}H NMR ($CDCl_3$, δ, ppm)	MS (EI, *m/z* (M^+))
		MW (min)	Thermal (h)	MW	Thermal				
4a	$C_{16}H_{12}N_2OS$ (280)	6	4	82	32	225	3320, 3050, 1690, 1620, 1600,1500, 1468, 1200, 1180 cm^{-1}	δ 2.1 (s, 1H, -NH-), 4.8 (s, 1H, -C=CHAr), 7.2-7.4 (m, 10 H, Ar-H)	280 (M^+)
4b	$C_{16}H_{11}NOSCl$ (314.5)	7	5	81	32	240	3330, 3052, 1695, 1620, 1600, 1500, 1460, 1210, 1190 cm^{-1}	δ 2.4 (s, 1H, -NH-), 5.2 (s, 1H, -C=CHAr), 7.21-7.51 (m, 9H, Ar-H)	314.5(M^+)
4c	$C_{16}H_{12}N_2O_2S$ (296)	5	3	84	34	130	3320, 3050, 2530, 1685, 1618, 1600, 1502, 1469, 1205, 1185 cm^{-1}	δ 2.2 (s, 1H, -NH-), 4.4 (s, 1H, -OH exchangeable with D_2O), 4.78 (s, 1H, -C=CHAr), 6.9-7.4 (m, 9H, Ar-H)	296.12(M^+)
4d	$C_{17}H_{14}N_2O_2S$ (310)	5	3	88	35	210	3320, 3050, 3000, 1690, 1620, 1600, 1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 2.3 (s, 1H, -NH-), 3.3 (s, 3H, -OCH_3), 4.82 (s, 1H, -C=CHAr), 7.07-7.76 (m, 9H, Ar-H)	310(M^+).
4e	$C_{16}H_{11}N_3O_3S$ (325)	8	6	80	30	245	3330, 3045, 1690, 1625, 1600, 1504, 1470, 1210, 1190 cm^{-1}	δ 2.5 (s, 1H, -NH-), 4. 2 (s, 1H, -C=CHAr), 6.92-7.40 (m, 9H, Ar-H)	325.13(M^+)
4f	$C_{17}H_{14}N_2O_3S$ (326)	5	3	87	34	195	3320, 3050, 3000, 2520, 1690, 1620,	δ 2.1 (s, 1H, -NH-), 3.3 (s,3H, OCH_3), 4.4 (brs,	326.10(M^+)

							1600, 1500, 1468, 1200, 1180, 1120 cm^{-1}	1H, -OH exchangeable with D_2O), 4. 8 (s, 1H, -C=CHAr), 7.1-7.9 (m, 8H, Ar-H)	
4g	$C_{17}H_{14}N_2OS$ (294)	6	4	82	31	230	3320, 3050, 2960, 1690, 1620, 1600, 1500, 1468, 1200, 1180 cm^{-1}	^1H NMR ($CDCl_3$): δ 1.32 (s, 3H, $-CH_3$), 2.1 (s, 1H, -NH-), 4. 8 (s, 1H, -C=CHAr), 7.2-7.4 (m, 9H, Ar-H)	294.16(M^+)
4h	$C_{17}H_{13}N_2OSCl$ (328.5)	7	6	83	33	248	3330, 3052, 2960, 1695, 1620, 1600, 1500, 1460, 1210, 1190 cm^{-1}	δ 1.31 (s, 3H, $-CH_3$), 2.4 (s, 1H, -NH-), 5.2 (s, 1H, -C=CH Ar), 7.21-7.51 (m, 8H, Ar-H	328.10(M^+)
4i	$C_{17}H_{14}N_2O_2S$ (310)	6	4	86	33	180	3320, 3050, 2950, 2540, 1685, 1618, 1600, 1502, 1469, 1205, 1185 cm^{-1}	δ 1.32 (s, 3H, $-CH_3$), 2.2 (s, 1H, -NH-), 4.4 (s, 1H, -OH exchangeable with D_2O), 4. 78 (s, 1H, -C=CHAr), 6.9-7.4 (m, 8H, Ar-H)	310.14(M^+)
4j	$C_{18}H_{16}N_2O_2S$ (324)	6	4	87	34	220	3320, 3050, 3000, 2950, 1690, 1620, 1600, 1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 1.31 (s, 3H, $-CH_3$), 2.3 (s, 1H, -NH-), 3.3 (s, 3H,$-OCH_3$), 4.82 (s, 1H, -C=CHAr), 7.07-7.76 (m, 8H, Ar-H	324.18(M^+)
4k	$C_{17}H_{13}N_3O_3S$ (339)	8	6	81	36	248	3330, 3045, 2960, 1690, 1625, 1600, 1504, 1470, 1210, 1190 cm^{-1}	δ 1.33 (s, 3H, $-CH_3$), 2.5(s, 1H, -NH-), 4. 2 (s, 1H, -C=CHAr), 6.92-7.40 (m, 8H, Ar-H	339.16(M^+)
4l	$C_{18}H_{16}N_2O_3S$ (340)	5	4	88	35	200	3320, 3050, 3000, 2960, 2520, 1690, 1620, 1600, 1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 1.30(s, 3H, $-CH_3$), 2.1(s, 1H, -NH-), 3.3 (s, 3H, $-OCH_3$), 4.4 (s, 1H, -OH exchangeable with D_2O), 4. 8 (s, 1H,-C=CHAr),7.1-7.9(m, 7H, Ar-H)	340.15(M^+)

Compd	**Ar'**	**Mol.Formula[a] (Mol. wt)**	**Yield [b] (%) MW**	**m.p. (^oC)**	**IR (KBr, υ cm^{-1})**	**^1H NMR (400 MHz,$CDCl_3$, δ, ppm)**	**MS (EI, *m/z* (M^+)**
5a	C_6H_5	$C_{18}H_{16}N_4OS$ (336)	78	112	3320, 3050, 1690, 1640, 1600,1500, 1468, 1200, 1180 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, $-COCH_3$), 3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.27 (m, 10 H, Ar-H)	336.10(M^+)
5b	4-Cl-C_6H_4	$C_{18}H_{15}ClN_4OS$ (370.5)	76	122	3330, 3050, 1690, 1640, 1600,1500, 1468, 1200, 1180 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, $-COCH_3$), 3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.22 (m, 9 H, Ar-H)	370.5(M^+)
5c	4-HO-C_6H_4	$C_{18}H_{16}N_4O_2S$ (352)	80	124	3320, 3050, 2900, 2560, 1690, 1640, 1600,1500, 1468, 1200, 1180 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, $-COCH_3$), 3.6 (m, 1H, H-4), 5.0 (brs, 1H, ArOH exchangeable with D_2O), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01 (m, 9 H, Ar-H)	352.14(M^+)
5d	4-MeO-	$C_{19}H_{18}N_4O_2S$	82	119	3320, 3050, 2930, 1690, 1640,	δ 2.0 (d, 1H, *J*= 2.5 Hz, -	366.16(M^+)

	C_6H_4	(366)			1600,1500, 1468, 1200, 1180, 1120 cm^{-1}	NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3),5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01 (m, 9 H, Ar-H)	
5e	2-NO_2-C_6H_4	$C_{18}H_{15}N_5O_3S$ (381)	73	115	3320, 3050, 1690, 1640, 1600,1500, 1468, 1200, 1180, cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-8.14 (m, 9 H, Ar-H)	381(M^+)
5f	3-MeO, 4-HO-C_6H_3	$C_{19}H_{18}N_4O_3S$ (381)	86	130	3320, 3050, 2930, 2560, 1690, 1640, 1600,1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3), 5.0 (brs, 1H, ArOH exchangeable with D_2O), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01 (m, 8H, Ar-H)	381.15(M^+)
5g	C_6H_5	$C_{19}H_{18}N_4OS$ (350)	80	110	3320, 3050, 2930, 1690, 1640, 1600,1500, 1468, 1200, 1180, cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.21 (m, 9H, Ar-H)	350.10(M^+)
5h	4-Cl-C_6H_4	$C_{19}H_{17}ClN_4OS$ (384)	85	118	3330, 3050, 2940, 1690, 1640, 1600,1500, 1468, 1200, 1180, cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.22(m, 8H, Ar-H).	384.5(M^+)
5i	4-HO-C_6H_4	$C_{19}H_{18}N_2O_2S$ (366)	86	123	3320, 3050, 2940, 2900, 2560, 1690, 1640, 1600,1500, 1468, 1200, 1180, cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 5.0 (brs, 1H, ArOH exchangeable with D_2O),5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01(m, 8H, Ar-H).	366.14(M^+)
5j	4-MeO-C_6H_4	$C_{20}H_{20}N_4O_2S$ (380)	87	126	3320, 3050, 2930, 2900, 1690, 1640, 1600,1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01(m, 8H, Ar-H).	380.16(M^+)
5k	2-NO_2-C_6H_4	$C_{19}H_{17}N_5O_3S$ (395)	83	128	3320, 3050, 2930, 1690, 1640, 1500, 1468, 1200, 1180, cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3),3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-8.14(m, 8H, Ar-H).	395(M^+)
5l	3-MeO, 4-HO-C_6H_3	$C_{20}H_{20}N_4O_3S$ (395)	88	132	3320, 3050, 2930, 2900, 2560, 1690, 1640, 1600, 1500, 1468, 1200, 1180, 1120 cm^{-1}	δ 2.0 (d, 1H, *J*= 2.5 Hz, -NH-), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (m, 1H, H-4), 3.73 (s, 3H, -OCH_3), 5.0 (brs, 1H, ArOH exchangeable with D_2O), 5.1 (d, 1H, *J*= 3.2 Hz, H-8), 6.46-7.01(m, 7H, Ar-H).	395.15(M^+)

Compd	Ar	Ar'	Mol.Formula[a] (Mol. wt)	Time MW (min)	Yield[b] (%) MW	m.p. (^oC)	^1H NMR (400 MHz,$CDCl_3$, δ, ppm)	^{13}C NMR (100 MHz,$CDCl_3$, δ, ppm)	MS (EI, m/z (M^+)
6a	C_6H_5	C_6H_5	$C_{23}H_{24}N_4O_5S$ (468)	4	78	110	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J= 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3", 2 x H-5'), 3.92 (m, 1H, H-4'), 4.96 (d, 1H, J= 4.2 Hz, H-1'), 5.1 (d, 1H, J= 3.2 Hz, H-8), 6.46-7.12 (m, 10 H, Ar-H)	δ 125.3-142.4 (Aromatic carbons), 171(C=O), 155 (C=N-), 180.9 (C=S), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4 (C-8), 18.1 ($-COCH_3$).	468.15(M^+)
6b	C_6H_5	4-Cl-C_6H_4	$C_{23}H_{23}ClN_4O_5S$ (502)	5	77	120	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J= 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3", 2 x H-5'), 3.92 (m, 1H, H-4'), 4.96 (d, 1H, J= 4.2 Hz, H-1'), 5.1 (d, 1H, J= 3.2 Hz, H-8), 6.46-7.22 (m, 9 H, Ar-H)	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.3-140.5(Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4 (C-8), 18.1 ($-COCH_3$).	502.11(M^+)
6c	C_6H_5	4-OH-C_6H_4	$C_{23}H_{24}N_4O_6S$ (484)	5	80	116	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J= 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3", 2 x H-5'), 3.92 (m, 1H, H-4'), 4.96 (d, 1H, J= 4.2 Hz, H-1'), 5.0 (brs, 1s, Ar-OH exchangeable with D_2O),5.2 (d, 1H, J= 3.2 Hz, H-8), 6.46-7.01 (m, 9 H, Ar-H)	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.3-155.3 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4 (C-8), 18.1 ($-COCH_3$).	484.14(M^+)
6d	C_6H_5	4-OMe-C_6H_4	$C_{24}H_{26}N_4O_6S$ (498)	5	86	115	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J= 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'),3.72 (s, 3H, $-OCH_3$), 3.92 (m, 1H, H-4'), 4.96 (d, 1H, J= 4.2 Hz, H-1'), 5.1 (d, 1H, J= 3.2 Hz, H-8), 6.46-7.01 (m, 9 H, Ar-H)	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.3-160.0 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 56.0 ($-OCH_3$), 49.6 (C-4), 49.4 (C-8), 18.1($-COCH_3$).	498.5(M^+)
6e	C_6H_5	2-NO_2-C_6H_4	$C_{23}H_{23}N_5O_7S$ (513)	8	75	118	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.46-8.14 (m, 9 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.3-156.2 (Aromatic carbons), 85.3 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4 (C-8), 18.1($-COCH_3$).	513.13(M^+)
6f	C_6H_5	3-OMe, 4-OH-C_6H_3	$C_{24}H_{26}N_4O_7S$ (514)	5	86	125	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, $-COCH_3$), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.73 (s, 3H, $-OCH_3$), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.3-149.0 (Aromatic carbons), 85.2 (C-1'), 76.1 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'),56.3 ($-OCH_3$), 49.8(C-8),	514.15(M^+)

							Hz, H-1'), 5.0 (brs, 1s, Ar-OH exchangeable with D_2O), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.46-7.07 (m, 8 H, Ar-H).	49.6 (C-4), 18.1(-$COCH_3$).	
6g	4-Me-C_6H_4	C_6H_5	$C_{24}H_{26}N_4O_5S$ (482)	4	79	114	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.34-7.21 (m, 9 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.2-142.4 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4(C-8), 20.9 (-CH_3), 18.1(-$COCH_3$).	482.16(M^+)
6h	4-Me-C_6H_4	4-Cl-C_6H_4	$C_{24}H_{25}ClN_4O_5S$ (516)	5	77	124	δ 2.0 (brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.46-7.22 (m, 8 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.2-140.5 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4(C-8), 20.9 (-CH_3), 18.1(-$COCH_3$).	516.11(M^+)
6i	4-Me-C_6H_4	4-OH-C_6H_4	$C_{24}H_{26}N_4O_6S$ (498)	4	84	122	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.0 (brs, 1s, Ar-OH exchangeable with D_2O), 5.2 (d, 1H, J = 3.2 Hz, H-8), 6.46-6.95 (m, 8 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.5-155.5 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4(C-8), 20.9 (-CH_3), 18.1(-$COCH_3$).	498.14(M^+)
6j	4-Me-C_6H_4	4-OMe-C_6H_4	$C_{25}H_{28}N_4O_6S$ (512)	4	86	124	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.73 (s, 3H, -OCH_3), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.34-7.07 (m, 8 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),113.0-160.0 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 56.0 (-OCH_3), 20.9 (-CH_3), 18.1(-$COCH_3$).	512.17(M^+)
6k	4-Me-C_6H_4	2-NO_2-C_6H_4	$C_{24}H_{25}N_5O_7S$ (528)	8	80	130	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d, 1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.1 (d, 1H, J = 3.2 Hz, H-8), 6.34-7.60 (m, 8 H, Ar-H).	δ 180.9 (C=S), 171(C=O), 155 (C=N-),125.2-142.0 (Aromatic carbons), 85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 49.6 (C-4), 49.4(C-8), 20.9 (-CH_3), 18.1(-$COCH_3$).	528.16(M^+)
6l	4-Me-C_6H_4	3-OMe, 4-OH-C_6H_3	$C_{25}H_{28}N_4O_7S$ (528)	4	88	131	δ 2.0(brs, 3H, 3 x OH exchangeable with D_2O), 2.02 (s, 3H, -$COCH_3$), 2.35 (s, 3H, -CH_3), 3.6 (d,	δ 180.9 (C=S), 171(C=O), 155 (C=N-),116.5-140.9 (Aromatic carbons),	528.17(M^+)

1H, J = 3.2 Hz, H-4), 3.65-3.88 (m, 4H, H-2', H-3', 2 x H-5'), 3.73 (s, 3H, -OCH_3),3.91 (m, 1H, H-4'), 4.96 (d, 1H, J = 4.2 Hz, H-1'), 5.0 (brs, 1s, Ar-OH exchangeable with D_2O), 5.2 (d, 1H, J = 3.2 Hz, H-8), 6.34-6.81 (m, 7H, Ar-H).

85.2 (C-1'), 76.6 (C-3'), 76.3 (C-4'), 76.0 (C-2'), 61.9 (C-5'), 56.0 (-OCH_3), 49.7 (H-8), 49.6 (C-4), 20.9 (-CH_3), 18.1(-$COCH_3$).