Synthesis and Biological Evaluation of some Condensed Thieno [2, 3 D] Pyrimidines for Analgesic and Anti-inflammatory Activity.

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Abstract:

Pain and inflammation is the most common occurring disorder in human beings and mainly caused by bacterial infections. Though this is most prevalent disorder and many chemotherapeutic, analgesic and anti-inflammatory drugs prescribed many of them have side effects like gastric or intestinal ulceration, increased bleeding time due to inhibition of thromoboxane-A2. Thus there is need to develop agents having more potency at smaller dose and also less side effects. Hence the research work carried out by synthesizing some condensed thieno [2,3 *d*] pyrimidine compounds and same compounds were evaluated for an analgesic, anti-inflammatory activity. Amongst the title compounds synthesized, compounds [IVa-1, IVb-1] having bromine (halogen) as a substituent present on phenyl ring found to be having moderate analgesic and anti-inflammatory activity rather than other synthesized compounds compared with reference standard Diclofenac Sodium.

Key words: Condensed thieno [2, 3 d] pyrimidine compounds, analgesic and anti-inflammatory

Introduction:

Pain and inflammation is the most common complaint for which patients seek treatment. It is accompanied by pain, redness, heat and swelling. Prostaglandins are one of the inflammatory mediators formed by arachidonic acid cascade. Anti-inflammatory agents are believed to act by inhibiting COX-2 enzyme which is responsible for conversion of arachidonic acid into PGE2. Inhibition of this enzyme by all other nonselective NSAID's primarily responsible for number of side effects. Except *p*-Aminophenol derivatives, these drugs produce gastrointestinal side effects like gastric or intestinal ulceration, increased bleeding time etc.

Generally bacterial infections often produce pain and inflammation. In normal practice two group of agents (chemotherapeutic, analgesic and anti-inflammatory) are prescribed simultaneously. Unfortunately none of drug possesses these three activities in a single component. Literature revels that quinazolines and condensed quinazolines not only have potent antimicrobial activity[(1)] but also analgesic and anti-inflammatory activities.[(2)] Also recent reports have shown that thienopyrimidines (bioisostere of quinazolines) possess CNS, antibacterial[(3,4,5)] and analgesic and anti-inflammatory activities.[(6)] Thus in order to have efforts towards development and identification of new molecules by bioisostereic concept, some condensed thieno [2,3*d*] pyrimidines have been synthesized and evaluated for analgesic and anti-inflammatory activities as per the procedure mentioned below.

Experimental:

The required starting materials i.e 2-Amino, 3-Carbethoxy 4,5 disubstituted thiophenes (Ia-Ic) for synthesizing target molecules are synthesized by using Gewald reaction. Further, above synthesised 2-Amino,3-Carbethoxy 4,5 substituted thiophenes were cyclicised by using formamaide to give corresponding 4-Oxo derivatives (IIa-IIc)which were further converted into corresponding 4-chloro derivatives (IIIa-IIIc) by using DMF and POCl3. The target compounds (IVa-IVc) were synthesised by replacing 4 -Chloro group of componds (IIIa-IIIc) by various amines as depicted in below scheme of synthesis.

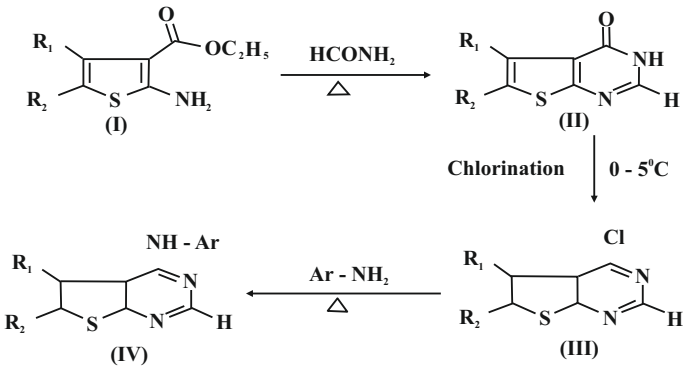


Figure no. 1: Synthesis scheme

Chemistry:

Synthesis of 4,5-Disubstituted-2-amino -3-carboethoxy thiophenes: (Ia-Ic)

1. Synthesis of 2-amino-3-carbethoxy-4, 5, 6, 7-tetrahydrobenzo (b) thiophene: (Ia). (Method A)

Cyclohexanone (9.8 g; 0.1 mole), sulfur (3.2g; 0.1 mole), ethyl cyanoacetate (11.3 g; 0.1 mole) and ethanol (20 ml) were mixed and stirred together. To this well stirred mixture diethyl amine (9.14 g; 0.125 mole) was added drop wise for ½ hour and stirring continued for another 3 hours at ambient temperature. The reaction mixture was kept in refrigerator over-night. Next day the solid separated was filtered and washed with 20 ml chilled 50% aqueous methanol. The product (15.52g;68.9% yield) having m.p. 111-1120C (1150C)1 was character-ized as 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(b)thiophene **(I*a*).**

Molecular formula	:	C11H15NO2S.
IR(KBr) cm -1	:	3414,3306(γNH); 3165, 3074, 2988, 1649(γCOOEt).
UV(MeOH) λ max	:	311.0nm.
TLC	:	Solvent system (benzene -4.5 ml: methanol - 2 drops) ;

Rf = 0.7.

2. Synthesis of 2-amino-3-carbethoxy-5-ethylthiophene: (I *b*). (Method B)

Butyraldehyde (7.2g; 0.1mole), sulfur (3.2g; 0.1mole), ethyl cyanoacetate (11.3g; 0.1mole) and dimethylformamide (15.2 ml) were stirred and maintained around 500C. Triethylamine (10.1g; 0.1mole) was added drop wise for ½ hour with stirring and stirring was continued at room temperature for 12 more hours. The reaction mixture was kept in refrigerator overnight. Next day the solid separated was filtered and washed with 20 ml chilled 50% methanol. The product (13.67g; 68.7% yield) having m.p. 62-63oC (730C)1 was characterized as 2-amino-3-carbethoxy-5-ethylthiophene **(I *b*).**

Molecular formula	:	C9H13NO2S.
IR(KBr) cm -1	:	3408,3306(γNH); 3167, 2966, 1660(γCOOEt).
UV(Me)λmax	:	305.2nm.
TLC	:	Solvent system (benzene - 4.5 ml: methanol- 2 drops) ;

Rf = 0.59.

3. Synthesis of 2-amino-3-carbethoxy-4,5-dimethylthiophene: (I*c*)

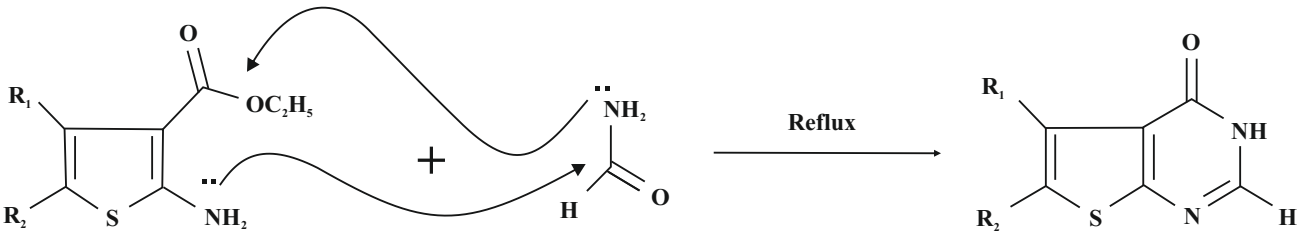
2-amino-3-carbethoxy-4, 5-dimethylthiophene (I*c*) was synthesized by above mentioned Method - Ausing 2 - Butanone (Ethylmethylketone). The product (12.87g; 64.7% yield) having m.p. 92-930C (91-920C)1 was characterized as 2-amino-3-carbethoxy-4, 5-dimethylthiophene (I*c*).

Molecular formula	:	C9H13NO2S.
IR(KBr) cm– 1	:	3425, 3312(γNH); 3155, 2984, 1657(γCOOEt).
UV(MeOH) λ max	:	310.4nm.
TLC	:	Solvent system (benzene - 4.5 ml: methanol- 2 drops);

Rf = 0.67.

Synthesis of 2-(*H*)-5, 6-disubstitutedthieno (2, 3-*d*) pyrimidin-4-(3*H*)-ones: (II*a-IIc*).

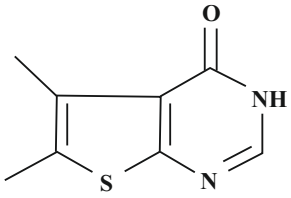
The thiophene *o*-amino esters **(I)** prepared above by the variants of Gewald reaction were cyclized with the „C-N‟ component of form amide at reflux temperature of form amide for 8-12 hours. The work up of reaction mixture yielded the cor responding 2(*H*) -5, 6-Disubstitutedthieno (2, 3-*d*) pyrimidine-4(3*H*) -ones in excellent yields **(II*a-IIc*).**



Ia; R^1,R^2 =-$(CH_2)_4$-
Ib; R^1=H;R^2=C_2H_5
Ic; R^1=R^2=CH_3

IIa; R^1,R^2 =-$(CH_2)_4$-
IIb; R^1=H;R^2=C_2H_5
IIc; R^1=R^2=CH_3

The synthesized 2(*H*)-5, 6-disubstitutedthieno (2, 3-*d*) pyrimidin-4(3*H*) ones **(II*a-IIc)*** compounds are pale yellow to brown crystalline solids. They are insoluble in water, alcohol and benzene but sparingly soluble in chloroform and dimethylformamide. They are high melting solids (m.p.200-250oC). The IR (KBr) of these compounds reveal prominent (γCONH) vibration around 1650-1665 cm-1. Given below is the IR spectra of a 2(*H*)-5, 6-dimethylthieno (2, 3-*d*) pyrimidin-4(3*H*)-ones as specimen.



Reaction of 2-amino-3-carbethoxy-4,5,6,7- t e t rahydrobenzo (b) thiophene wi th formamide:

2-Amino-3-carbethoxy-4, 5, 6, 7-tetrahydrobnzo (*b*) thiophene **(I*a*)** (5.0gm; 0.02moles) and form amide (15 ml) were refluxed for 8 to 10 hrs. The reaction mixture was cooled to room temperature and poured in ice water. The solid obtained was filtered, washed with chilled water and dried. The crude product on recrystallisation from methanol–dimethylformamide yielded (4.0gm; 87.5%yield.) m.p 208-210 0C and was characterized as 2-(*H*)-5, 6, 7, 8-tetrahydrobenzo (*b*) thieno [2, 3-*d*] pyrimidin-4-(3*H*)-one

Molecular formula : C10H11N2OS.

IR(KBr) cm -1 : 1662(γCOONH); 1635(γC=N); 720(γC-S).

UV(MeOH) λ max : 307nm.

TLC : Solvent system (chloroform - 5 ml: methanol -2 drops);

Rf = 0.62.

Similarly reaction of 2-amino-3-carbethoxy-6-ethylthiophene and 2-amino-3-carbethoxy-4, 5-dimethylthiophene with form amide is carried out and worked up as above. The crude product on recrystallisation from methanol–dimethylformamide yielded products **(II*a*-IIc)**.

Synthesis of 2-(*H*)-4-Chloro-5,6-disubstitutedthieno(2,3-*d*)pyrimidines (III*a*-IIIc)

Chlorination of 2-(*H*)-5,6,7,8-tetrahydrobenzo (*b*) thieno[2,3-d]pyrimidin-4-(3*H*)-one:

To a well stirred and cold solution of 2-(*H*)-5,6,7,8-tetrahydrobenzo(*b*) thieno [2,3-*d*] pyrimidin-4-(3*H*)-one **(II*a*)** (5.0g;0.022mole)in dry dimethylformamide(40ml) contained in a conical flask fitted with guard tube, placed in an ice salt bath maintained at temperature 0-50 C was added drop wise phosphorusoxychloride (10ml) for ½ hour. The reaction mixture was stirred at 0-50C for further one hour and then was kept at room temperature for one hour. The reaction mixture was kept overnight & on the next day was poured on crushed ice and allowed to stand for one hour. The solid separated was filtered and washed with chilled water, dried and recrystallized from n-hexane to yield (5.5g; 87.0 % yield) having m.p. (114-1150C) characterized as a 2-(*H*)-4-Chloro-5,6,7,8-tetrahydrobenzo(*b*) thieno [2,3-*d*]pyrimidine

Molecular formula : C10H9ClN2S.

IR(KBr) cm -1 : 2936(γCH);800,707(γC-Cl).

UV(MeOH) λ max : 292.0nm.

TLC : Solvent system (benzene- 4.5 ml: methanol- 2 drops);

Rf = 0.71.

Similarly Chlorination of 2-(*H*)-6-ethylthieno [2, 3- *d*] pyrimidin-4-(3*H*)-one and 2-(*H*)-5, 6-dimethylthieno [2, 3-*d*] pyrimidin-4-(3*H*)-one carried out as per above procedure to yield (IIIb-IIIc)

Synthesis of 2-(H)-4-Arylamino-5,6-disubstitutedthieno [2,3-d]pyrimidines (IVa-1-3 to IVc-1).

Synthesis of 4-(4-Bromophenyl) amino-5,6,7,8-terahydrobezo(b)thieno[2,3-*d*]pyrimidine. (IVa-1)

To a solution of 2-(*H*)-4-Chloro-5,6,7,8-tetrahydrobenzo(*b*) thieno [2,3-*d*] pyrimidin-4-(3*H*)-one **(III*a*)** (5.0g;0.022mole)in isopropanol (40ml) contained in a conical flaskwas added p-Bromoaniline(8.0g, 0.04 mole),and the reaction mixture was refluxed for 10 hrs. After completion of reaction, it is poured in crushed ice to give crystaline product i.e4-(4-Bromophenyl) amino-5,6,7,8-terahydrobezo z(*b*)thieno[2,3-*d*]pyrimidine.. Recrystallization carried out by using chloroform and isopropanol. % yield was found to be 97%, M.P. 158-1600c.

Molecular formula : C16H14BrN3S

IR(KBr) cm -1 : 502(γC-Br); 3450(γNH).

UV(MeOH) λ max : 313.2nm.

TLC : Solvent system (benzene- 4.5 ml: methanol- 2 drops)

Rf = 0.7

By following similar procedure as mentioned above 4-(4-Methylphenyl) amino-5,6,7,8-terahydrobezo(*b*) thieno [2,3-*d*]pyrimidine**(IVa-2)** and 4-(4-Methoxyphenyl) amino-5,6,7,8-terahydrobezo(*b*) thieno [2,3-*d*]pyrimidine**(IVa-3)** compounds have been synthesized.

Synthesis of 4-(4-Bromophenyl) amino-6-ethylthieno[2,3-*d*] pyrimidine.

To a solution of 2-(*H*)-4-Chloro-6-ethylthieno[2,3-*d*]pyrimidine **(III*b*)** (5.0g;0.022mole)in isopropanol (40ml) contained in a conical flaskwas added p-Bromoaniline(8.0g, 0.04 mole),and the reaction mixture was refluxed for 10 hrs. After completion of reaction, it is poured in crushed ice to give crystaline product i.e 4-(4-Bromophenyl) amino-6-ethylthieno[2,3-*d*] pyrimidine**.** Recrystallization carried out by using chloroform and methanol. % yield was found to be 96%, M.P. 234-2380c.

Molecular formula : C14H12BrN3S

IR(KBr) cm -1 : 3323(γNH);600 (γC-Br).

UV(MeOH) λ max : 307.6nm.

TLC : Solvent system (benzene- 4.5 ml: methanol- 2 drops):

Rf = 0.6

By following similar procedure as mentioned above 4-(4-Methylphenyl) amino-6-ethylthieno[2,3-*d*] pyrimidine and 4-(4-Methoxyphenyl) amino-6-ethylthieno[2,3-*d*] pyrimidine com-pounds have been synthesized.

Synthesis of 4-(4-Bromophenyl) amino-5,6-dimethylthieno[2,3-*d*]pyrimidine

To a solution of 2-(*H*)-4-Chloro-5,6-dimethylthieno[2,3-*d*]pyrimidine **(IIIc)**(5.0g;0.02mole)in isopropanol (40ml) contained in a conical flaskwas added p-Bromoaniline(8 g, 0.04 mole),and the reaction mixture was refluxed for 10 hrs. After completion of reaction, it is poured in crushed ice to give crystaline product i.e 4-(4-Bromophenyl) amino-5,6-dimethylthieno[2,3-*d*] pyrimidine .Recrystallization carried out by using chloroform and isopropanol % yield was found to be 67%, M.P. 222-224.

Molecular formula : C14H12BrN3S

IR(KBr) cm -1 : 3253(γNH);800(γC-Br).

UV(MeOH) λ max : 307.8 nm.

TLC : Solvent system (benzene-

5 ml : methanol- 2 drops)

Rf = 0.5

Biological Evaluation [9, 10, 11]**:**

The test compounds **(Iva-1 to IVc-1)** at two dose level (100 mg and 150 mg kg-1) were administered orally by using Diclofenac Sodium at a dose level of 20 mg kg-1 as a reference drug for comparison for both analgesic and anti-inflammatory activity. The results obtained were subjected to analysis by using one way ANOVA technique followed by Dunnet test.

1. **Analgesic activity:** Test for analgesic activity was performed by tail-flick technique using Wistar albino mice (25-30 g) of either sex selected by random sampling technique. Diclofenac Sodium at a dose level of 20 mg kg-1 was administered orally as a reference drug for comparison. The test compounds **(Iva-1, to IVc-1)** at two dose level (100 mg and 150 mg kg-1) were administered orally. The Basal reaction time in seconds was recorded at 15 min,30 min, 60min, 90 min. after treatment, and cut off time was 10 Sec.

2. **Anti-inflammatory activity:** Anti-inflammatory activity was evaluated by carrageenan induced paw edema test in rats. Diclofenac Sodium at a dose level of 20 mg kg-1 was administered orally as a reference drug for comparison. The test compounds **(IVa-1 to IVc-1)** at two dose level (100 mg and 150 mg kg-1) were administered orally. The paw volumes were measured with the help of Plethysmograph immediately before and 30 min, 1-3 hr after Carrageenan injection. % Inhibition of paw edema was calculated by using following formula :

Percent inhibition I = 100 [1-(a-x)/(b-y)]

Where

x= mean paw volume of rats before administration of carrageenan and test compounds or reference compound (test group),

a = the mean paw volume of rats after administration of carrageenan in the test group (drug treated),

b = the mean paw volume of rats after administration of carrageenan in the control group,

y = the mean paw volume of rats before administration of carrageenan in the control group

Result And Discussion:

Physical data of 4, 5-Disubstituted-2-amino- 3-carbethoxythiophenes (I*a-c*).

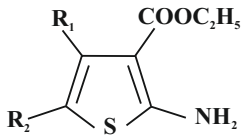


Table 1. Physical and chemical properties of ,5-Disubstituted-2-amino-3- carbethoxythiophenes (I*a-c*)

Compound No.	R_1	R_2	Yield (%) (Method)	M. P.(^{O}C) (Reported)[1]	Mol. formula (Solvent of Re-crystn.)
Ia	-(CH2)4-		68 (A)	110-112 (115)[1]	$C_{11}H_{15}NO_2S$ (*E*)
Ib	H	C_2H_5	68 (B)	62-63 (73)[1]	$C_9H_{13}NO_2S$ (*E*)
Ic	CH_3	CH_3	64 (A)	92-93 (91-92)[1]	$C_9H_{13}NO_2S$ (*E*)

Physical data of 2(*H*)-5,6-disubstituted(2,3-*d*)pyrimidin-4(3*H*)ones(II*a-c*).

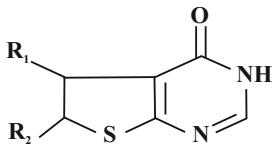


Table 2. Physical and chemical properties of 2(*H*)-5,6-disubstituted(2,3-*d*)pyrimidin-4(3*H*) ones(II*a-c*).

Compd No.	R1	R2	Yield (%)	M. P.(oC)	Mol. formula (Solvent of Recrystn.)
IIa	-(CH2)4-		87	208-210	$C_{10}H_{11}N_2OS$ (*M-D*)
IIb	H	C_2H_5	92	195 –197	$C_8H_8N_2OS$ (*M-D*)
IIc	CH_3	CH_3	68	192-193	$C_8H_8N_2OS$ (*M-D*)

M= Methanol; D =N,N- Dimethylformamide.

III. Physical data of 2-(*H*)-4-Chloro-5,6-disubstitutedthieno(2,3-*d*)pyrimidines(III*a-c*).

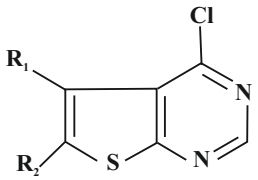
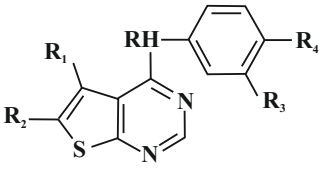


Table 3. Physical and chemical properties of 2-(*H*)-4-Chloro-5,6-disubstitutedthieno(2,3-*d*) pyrimidines(III*a-c*)

Compd.No.	R1	R2	Yield (%)	M. P.(oC)	Mol. formula (Solvent of Recrystn.)
IIIa	-(CH2)4-		87	114-115	$C_{10}H_9ClN_2S$ (*H*)
IIIb	H	C_2H_5	71	52 -54	$C_8H_7ClN_2S$ (*H*)
IIIc	CH_3	CH_3	89	153-155	$C_8H_7ClN_2S$ (*C*)

H= Hexane; *C =Chloroform*

IV. Physical data of 2(*H*)-4-Arylamino-5,6-disubstitutedthieno(2,3-*d*)pyrimidines (IVa-1 to IVc-1).



Compd.No.	R_1	R_2	R_3	R_4	Yield (%)	M.P. ^{0}C.	Mol. Formula (Solvent of Recrystn)
IVa-1	-$(CH_2)_4$-		H	Br	97	158-160	$C_{16}H_{14}BrN_3S$ (I-*C*)
IVa-2	-$(CH_2)_4$-		H	Ch_3	97	141-143	$C_{17}H_{17}N_3S$ (*I*)
IVa-3	-$(CH_2)_4$-		H	OCH_3	78	145-147	$C_{17}H_{17}ON_3S$ *(I)*
IVb-1	H	C_2H_5	H	Br	96	234-238	$C_{14}H1_{12}BrN_3S$ (M-C)
IVb-2	H	C_2H_5	H	CH_3	98	145-148	$C_{15}H15ON3S$ (*I*)
IVb-3	H	C_2H_5	H	OCH_3	92	138-140	$C_{15}H_{15}ON_3S$ *(I)*
IVc-1	CH_3 Ch_3		H	Br	67	222-224	$C_{14}H_{12}BrN_3S$ (*I-C*)

Spectral data of 4,5-Disubstituted-2-amino-3-carbethoxythiophenes(Ia-Ic).

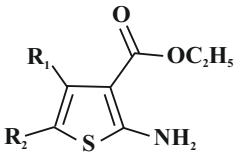


Table 4. Physical and chemical properties of 4,5-Disubstituted-2-amino-3- carbethoxythiophenes(Ia-Ic).

Compd.No.	R_1	R_2	UVλmax (nm) Methanol	I.R. (KBr) cm^{-1}
Ia	$-(CH_2)_4-$		311	3414, 3306 (g_{NH}) ; 3165,3074,2988, 1649(g_{COOEt}).
Ib	H	C_2H_5	305.2	3408, 3306 (γ_{NH}); 3167, 2966,1660(γ_{COOEt}).
Ic	CH_3	Ch_3	310.4	3425, 3312 (γ_{NH}) ; 3155,2984,1657(γ_{COOEt}).

VI. Spectral data of 2(*H*)-5,6-disubstitutedthieno(2,3-*d*)pyrimidin-4(3*H*)ones(II*a-c*).

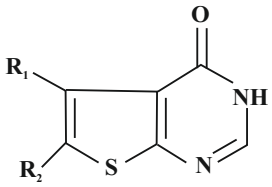


Table 5. Spectral data of 2(*H*)-5,6-disubstitutedthieno(2,3-*d*)pyrimidin-4(3*H*)ones(II*a-c*)

Compd.No.	R_1	R_2	UVλmax (nm) Methanol	I.R. (Kbr) cm^{-1}
IIa	$-(CH_2)_4-$		307	1662(γ_{COONH});1635 ($\gamma_{C=N}$);720(γ_{C-S}).
IIb	H	C_2H_5	298	1664(γ_{COONH});703(γ_{C-S}).
IIc	Ch_3	Ch_3	305.5	1662(γ_{COONH});641(γ_{C-S}).

VI . Spectral data of 2(*H*)-4-Chloro-5,6-disubstitedthieno(2,3-*d)*pyrimidines (III*a-c*).

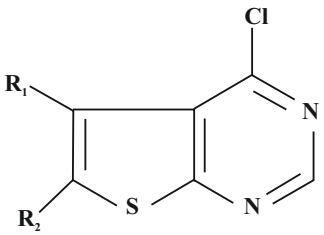


Table 6. Spectral data of 2(*H*)-4-Chloro-5,6-disubstitedthieno(2,3-*d)*pyrimidines (III*a-c*).

Compd.No.	R_1	R_2	UV λmax(nm) Methanol	I.R. (Kbr) cm^{-1}
IIIa	$-(CH_2)_4-$		292.0	2936(γ_{CH});800,707(γ_{C-Cl}).
IIIb	H	C_2H_5	279.0	2931(γ_{C-H});719(γ_{C-Cl}).
IIIc	CH_3	CH_3	295.0	2923(γ_{CH});709(γ_{C-CL}).

I. Spectral data of 2(*H*)-4-Arylamino-5,6-disubstitutedthieno(2,3-*d*)pyrimidines (IVa-1to IV c-1).

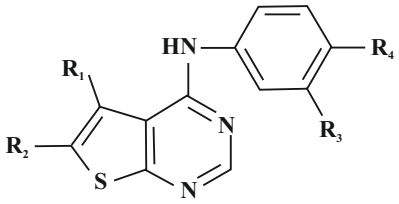


Table 7. Spectral data of 2(*H*)-4-Arylamino-5,6-disubstitutedthieno(2,3-*d*)pyrimidines (IVa- 1to IV c-1)

Sr.No	R_1	R_2	R_3	R_4	Uvλmax nm I	Rcm^{-1}I
Va-1	-$(CH_2)_4$-		H	Br	313.2	502(γ_{C-Br}); 3450(γ_{NH}).
IVa-2	-$(CH_2)_4$-		H	Ch_3	313.2	3423(γ_{NH}); 2871, 2933 ($\gamma_{CH\ Ch3}$).
IVa-3	-$(CH_2)_4$-		H	OCH_3	314.8	3454 (γ_{NH}); 1243(γ_{C-O})
IVb-1	H	C2H5	H	Br	307.6	3323 (γ_{NH}); 600 (γ_{C-Br}).
IVb-2	H	C2H5	H	CH_3	304.8	3250(γ_{NH}), 2975($\gamma_{CH\ Ch3}$).
IVb-3	H	C2H5	H	OCH_3	299.8	3305(γ_{NH});1244, 1045 (γ_{C-O-C}).
IVc-1	CH_3CH_3		H	Br	307.8	3253(γ_{NH}); 1055(γ_{C-Br}).

Pharmacological Sreening
Biological Evaluation:

Table 8. Evaluation of title compounds for analgesic activity by tail-flick technique.

Group	Treatment	Reaction Time (Sec.)	
		Basal Reaction time	At 1 hr
Control	2% Gum acacia	2.14±0.05	2.03±0.08
Standard	Diclofenac Sodium(20mg/kg)	2.54±0.06	8.95±0.05**
IVa-1	100 mg/kg	2.05±0.05	5.23*0.05±
IVa-1	150mg/kg	1.89±0.05	6.72±0.06*
IVa-2	100 mg/kg	2.99±0.06	4.02±0.06
IVa-2	150mg/kg	1.86±0.06	4.89±0.06*.
IVa-3	100 mg/kg	2.63±0.06	3.02±0.06
IVa-3	150mg/kg	2.19±0.08	3.97±0.07
IVb-1	100 mg/kg	2.01±0.08	4.98±0.07*
IVb-1	150mg/kg	2.29±0.05	6.41±0.08**
IVb-2	100 mg/kg	2.98±0.05	5.02±0.05
IVb-2	150mg/kg	2.00±0.07	4.34±0.06
IVb-3	100 mg/kg	1.89±0.07	3.21±0.06
IVb-3	150mg/kg	2.26±0.07	4.01±0.08
IVc-1	100 mg/kg	2.71±0.08	3.75±0.05
IVc-1	150mg/kg	2.08±0.08	4.26±0.08

Results are expressed as mean ± SEM. *p > 0.05, **p <0.01 as compared to control

Figure no. 2 Evaluation of title compounds for analgesic activity by tail-flick technique.

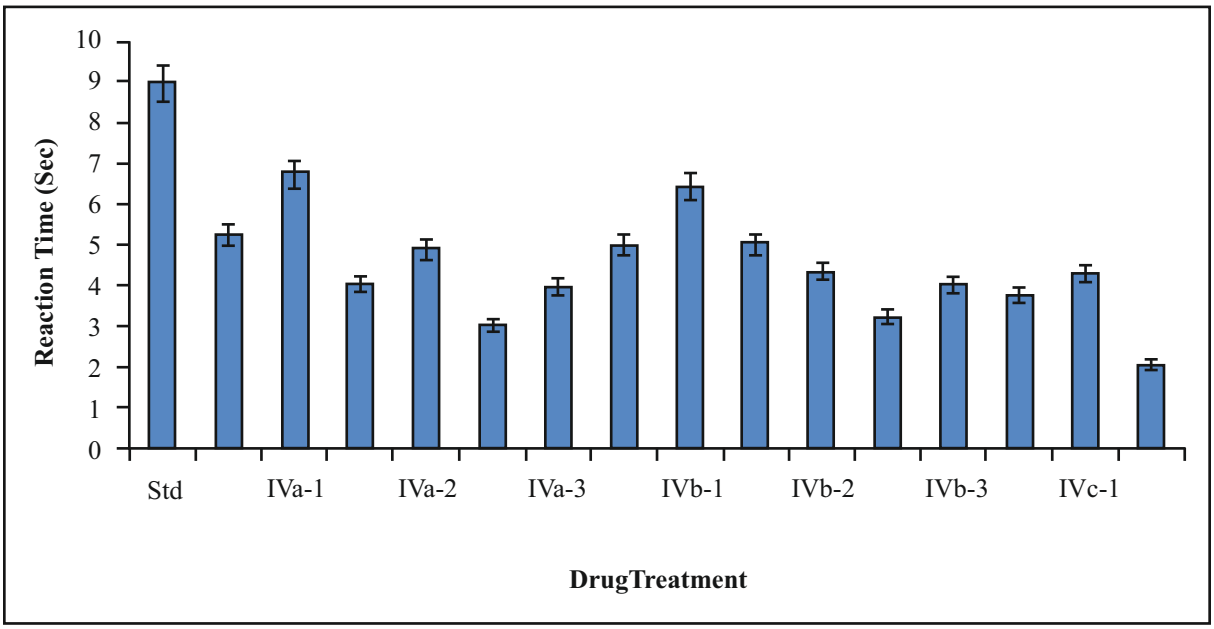
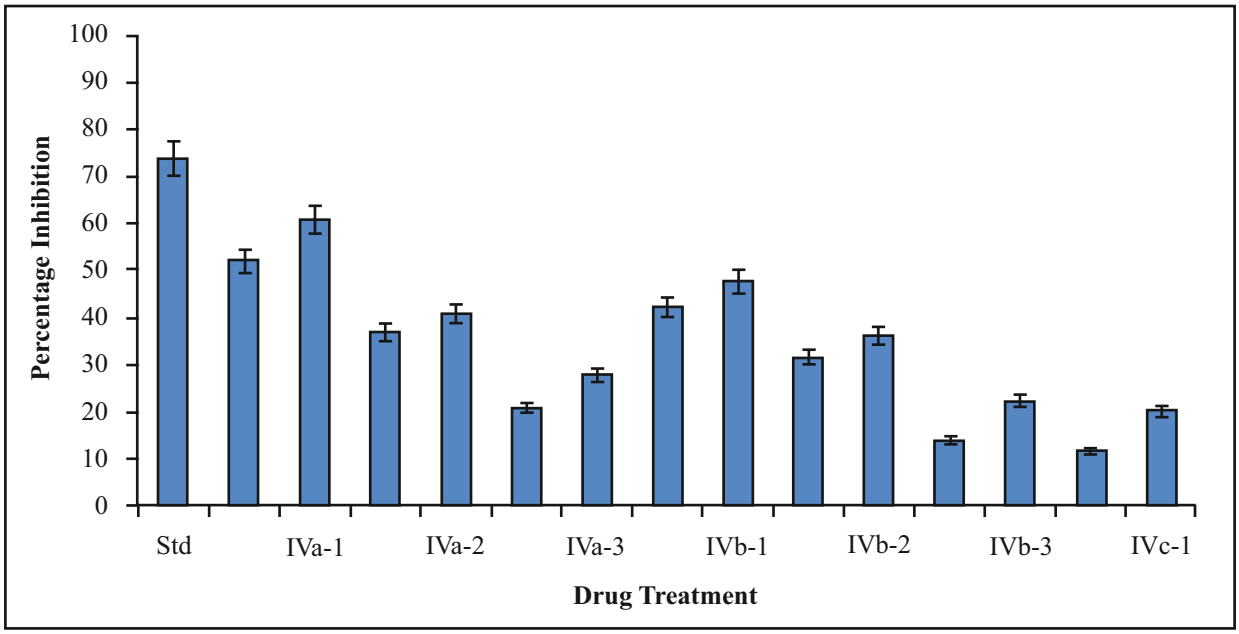


Table 9. Evaluation of title compounds for Anti-inflammatory activity by rat paw edema method.

Group	Treatment	Change in Paw volume (ml)	
		At 3rd hr	% Inhibition
Control	2% Gum acacia	1.30±0.08	0
Standard	Diclofenac Sodium(20mg/kg)	0.34±0.06**	73.85
IVa-1	100 mg/kg	0.62 ±0.06*	52.03
IVa-1	150mg/kg	0.51 ±0.07**	60.77
IVa-2	100 mg/kg	0.82±0.05	36.93
IVa-2	150mg/kg	0.77±0.06*	40.77
IVa-3	100 mg/kg	1.03±0.05	20.77
IVa-3	150mg/kg	0.94±0.05	27.70
IVb-1	100 mg/kg	0.68±0.05**	47.70
IVb-1	150mg/kg	0.55±0.06**	42.30
IVb-2	100 mg/kg	0.89±0.06	31.54
IVb-2	150mg/kg	0. 83±0.06*	36.16
IVb-3	100 mg/kg	1.12±0.06	13.85
IVb-3	150mg/kg	1.01±0.06	22.31
IVc-1	100 mg/kg	1.15±0.05	11.54
IVc-1	150mg/kg	1.04±0.05	20.00

Results are expressed as mean ± SEM. *p > 0.05, **p <0.01 as compared to control

Figure no. 3 Evaluation of title compounds for Anti-inflammatory activity by rat paw edema method.



Conclusion:

Many of the chemotherapeutic, analgesic and anti-inflammatory drugs that are prescribed have side effects like gastric or intestinal ulceration, increased bleeding time due to inhibition of thromoboxaneA_2 as mentioned earlier. Thus based on bioisosteric concept, 2(*H*)-4- Arylamino-5,6-disubstitutedthieno(2,3 -*d*) pyrimidines (IVa-1 to IV c-1)have been synthesized and evaluated for analgesic activity by Tail-flick technique using Wistar albino mice and for anti-inflammatory activity by using carrageenan induced paw edema test in rats. Diclofenac Sodium at a dose level of 20 mg $kg^{-1}$was used as a reference compound for both activities. Compounds with Cyclohexanone ring fused and Ethyl at 5^{th} position of thiophene ring and having bromine (halogen) as a substituent present on phenyl ring ,which is attached at 4^{th} position of 5,6-disubstitutedthieno[2,3-*d*] pyrimidines nucleus, were found to be having moderate analgesic and anti-inflammatory activity rather than other synthesized compounds compared with reference standard Diclofenac Sodium.

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Conflict of Interest: Nil

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