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Synthesis and QSAR Studies in 2-(*N*-aryl-*N*-aroyl)amino-4,5-dihydrothiazole Derivatives as Potential Antithrombotic Agents☆

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Abstract—A series of 2-(*N*-aryl-*N*-aroyl)amino-4,5-dihydrothiazole derivatives have been synthesized via cyclocondensation of *N*-aryl thioureas with 2-bromoethylamine hydrobromide followed by the reaction of the product thus obtained with aroyl chlorides. Title compounds were evaluated for their antithrombotic activity in vivo in mice where one of these compound **29** provided 65% protection as compared to 77% protection offered by the standard *Indomethacin*. Quantitative Structure–Activity Relationship (QSAR) studies were performed on these compounds using physicochemical (hydrophobic, electronic, steric) parameter as independent and antithrombic activity as dependent parameter, where antithrombotic activity correlated best ($r > 0.8$) with electronic parameters ($\mathcal{F}$, σ or μ) having high statistical significance $> 99.9\%$ ($F_{2,22} > 15.0$; $F_{2,22\alpha:0.001} = 11.0$) suggesting that hydrophobic, steric and resonance factors are insignificant in this set of molecules for the activity.

Introduction

The cardiovascular system disorders related diseases are the prime cause of mortality and morbidity in the today's world leading towards major socio-economic consequences. Controlled activation of blood coagulation, that is haemostasis is necessary to prevent the blood loss after fatal injury, where as, uncontrolled activation could lead to vascular and arterial thrombosis, which in turn could result into various serious thromboembolic diseases and the balance between these two states is maintained by the thrombin,[1] key enzyme of the blood coagulation cascade. Thrombin is a multifunctional protein[2] and plays a key role in the activation of platelets. Once platelets are activated, they enhance their production many folds by activating thromboxane A_2.

Aspirin is still the standard reference compound[3] for long term oral treatment for antiplatelet activity, which has been attributed to its indirect thromboxane A_2 inhibition by acetylating the cyclooxygenase enzyme, but, in view of its non-selectivity to the platelets and ineffectivity for the preexisting clot, there is a need for more efficacious agent devoid of above limitations.[4,5] The choice of thromboxane A_2 synthase inhibitors (TxSI) or thromboxane A_2 receptors antagonists (TxRA) once considered to have several advantages[6,7] over aspirin in terms of selective nature of inhibition as well as accumulation of prostaglandin (PG) endoperoxides leading to the generation of platelet inhibitory and tissue protective prostaglandin (PG) endoperoxides, such as prostacyclin has not shown encouraging clinical results and hence none of the drugs under phase III trials could get the market approval. Hence, the search for new chemical entities (NCE's) for antiplatelet/antithrombotic activity is of current interest.[8]

Based on our earlier laboratory experiences and the literatures[9,10] where some thiazole containing moieties were reported to posses antithrombotic activity, it appeared of interest to explore pharmacophoric character of this relatively unexploited substituent for antithrombotic activity. Hence, the title compounds, 2-disubstitutedamino-4, 5-dihydrothiazoles incorporating this substructure along with hydrophobic phenyl rings were designed, synthesized and evaluated for antithrombotic

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activity in vivo in mice. Further, the 2-D Quantitative Structure Activity Relationship (QSAR) studies were performed using the Hansch (linear free energy relationship) approach[11] keeping physicochemical parameters [hydrophobic (π), electronic (σ, $\mathcal{R}$, $\mathcal{F}$, μ), steric (MR)] as an independent and antithrombotic activity as dependent parameter. The details of these studies are reported here.

Chemistry

The key intermediates *N*-arylthioureas (**3a–j**) required for the synthesis of 2-(*N*-aryl-*N*-aroyl)amino-4, 5-dihydrothiazoles (**5–29**) were synthesized by the two routes (Scheme 1). In the first route, substituted anilines (**1a–j**) were condensed with benzoylisothiocyanates followed by the selective hydrolysis of carbonyl group (>C=O) of the products (**2a–j**) thus formed with sodium hydroxide (NaOH) as per reported method.[12,13] In a few cases, the *N*-aryl thioureas (**3a–e**) along with byproduct, which had different R_f value on TLC from the starting material **2**, IR and ^{1}H NMR characteristics similar to the starting material **2** but with lower molecular mass ($M^+ - C_6H_5CSNH$) of less intensity unlike that of the starting material **2** (M^+) was obtained. In order to deduce their structure, byproduct crystals obtained in the case of aniline and 4-anisidine (**2a** and **2b** respectively) were investigated for their X-ray data which showed them to be benzamide derivative of aniline (**3′a**) and 4-anisidine (**3′b**). The structure of the byproduct (**3′a**) was also confirmed by unambiguous and simple synthesis involving condensation of aniline (**1a**) with benzoyl chloride and comparing the spectroscopic data of the product thus formed with **3′a** which were identical. The byproduct of type **3′** was formed in cases where the hydrolysis was not selective and hydroxide ion (HO^-) is free to attack on both, the carbonyl (>C=O) and thiocarbonyl (>C=S) groups. It was observed that ratio of the byproducts (**3′a–e**) depended on the electronegativity of the substituent group on the aniline (Table 1) and the group having high electron donating ability increased the amount of the byproduct. The plausible mechanism for the byproduct formation might be intramolecular carbon to carbon (C-to-C) migration of the substituted aniline group through a concerted pathway (Scheme 2).

Due to the above-mentioned complications, second route was adopted for the synthesis of the *N*-aryl thioureas (**3a–j**). In this route the substituted anilines (**1a–j**) were heated with ammonium thiocyanate in presence of hydrochloric acid as per literature method[14] to give the *N*-aryl thioureas (**3a–j**). Except for a few anilines containing strong electron withdrawing groups, this one step method in general was better than the previous one in terms of the cost, yield and time. Compounds **3a–j** were cyclocondensed with 2-bromoethylamine hydrobromide to give the five member stable endocyclic[15] 2-arylamino-4, 5-dihydrothiazoles (**4a–j**). Finally, the reaction of **4a–j** with aroyl chlorides in dry acetone or THF using triethyl amine as a base provided the title compounds 2-(*N*-aryl-*N*-aroyl)amino-4, 5-dihydrothiazoles (**5–29**)[16] in good to excellent yields (Scheme 1). The structures of the final products **5–29** were characterized by routine spectroscopic data and elemental analyses and finally confirmed by X-ray crystallographic structure (Fig. 1) of one such compound **9**.

Antithrombotic activity evaluation

Swiss mice (20–25 g, from CDRI animal colony) were used in a group of at least 10 animals each. Thrombosis was induced by infusion of a mixture of 15 μg collagen and 5 μg adrenaline in a volume of 100 μL into the tail vein of each mouse. This resulted either death or hind limb paralysis of 100% animals.

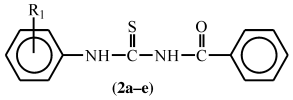
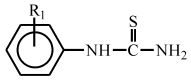
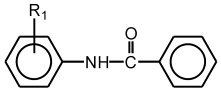
The compounds (**5–29**) were administered po (0.5 mM/kg/mice) 1 h prior to the thrombotic challenge. The antithrombotic effect of these compounds was assessed by the percent protection (%P) offered by these agents to mice from death or paralysis following thrombotic challenge using *Indomethacin* as a standard[17] (Table 2).

Results and Discussion

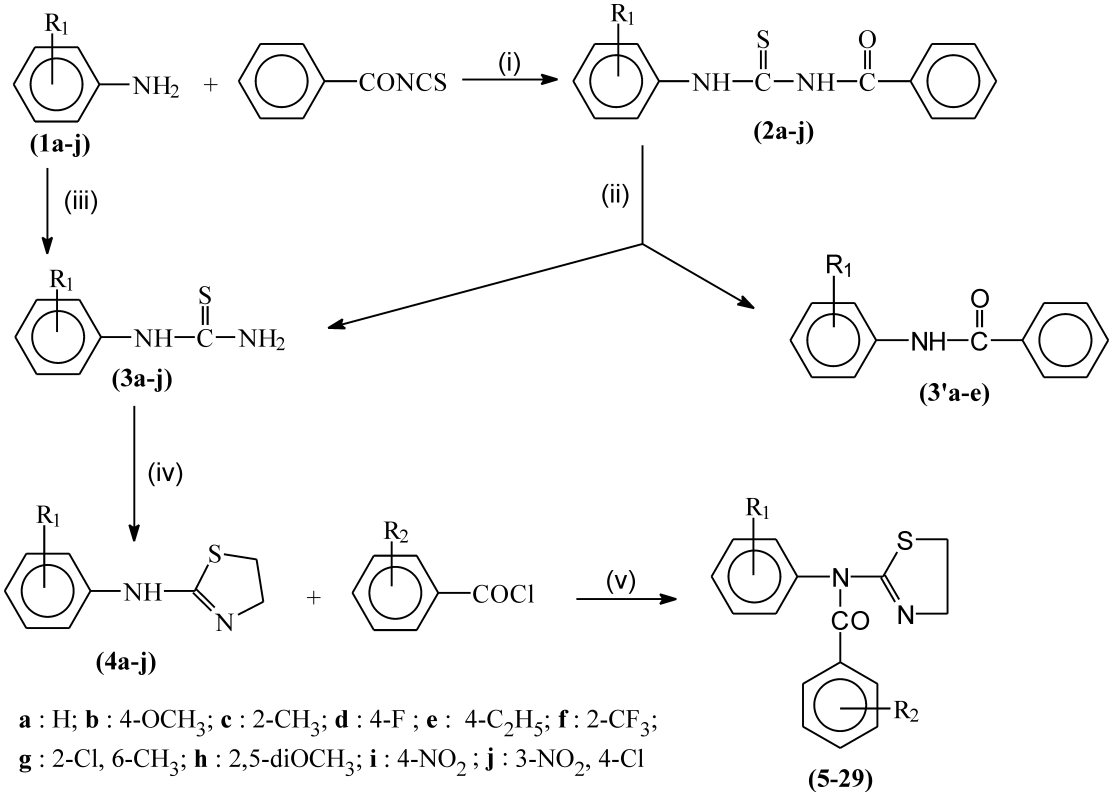
2-D QSAR analysis

Most of the title compounds **5–29** exhibited good antithrombotic activity in vivo in mice and among them the compounds **25**, **28** and **29** showed ≥50% protection in the order **29** > **28** = **25** for the thrombosis as compared to 77% protection offered by the standard *Indomethacin*. In order to gain insight into structure–activity relativity, these compounds were analyzed by physicochemical based QSAR (Hansch) approach using physicochemical parameters such as hydrophobic (π),

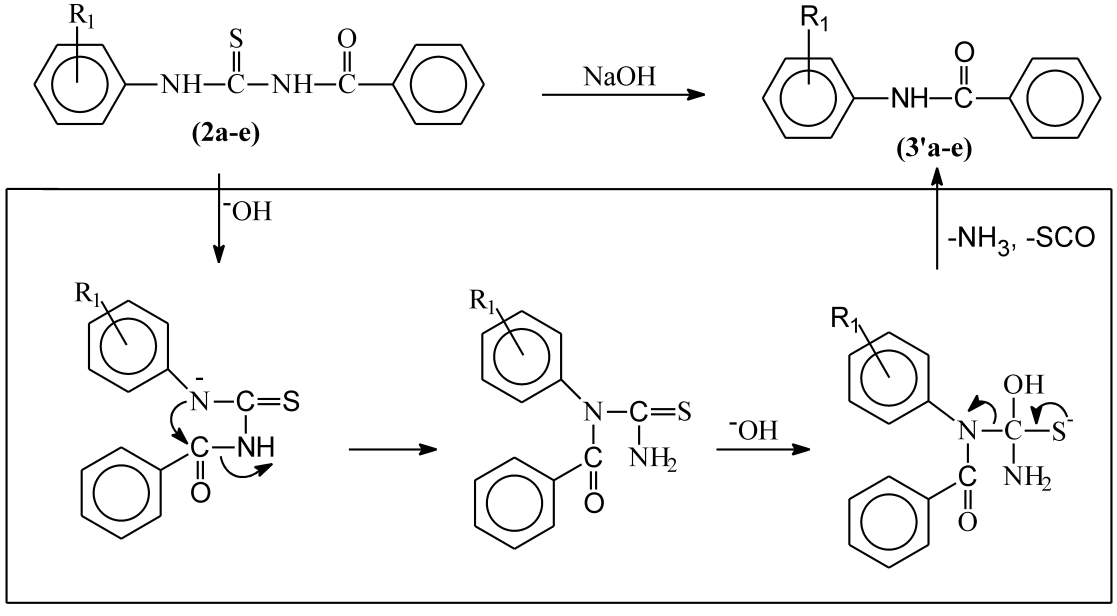
Table 1. Ratios of the expected *N*-aryl thioureas (**3**) and unexpected *N*-aryl benzamides (**3′**)

Compd no.	R_1	 (2a–e)	 (3a–e)	 (3′a–e)
		(g) (%)	(g) (%)	(g) (%)
a	H	7.5	3.24 (73)	1.60 (27)
b	4-OCH_3	5.0	1.74 (55)	1.58 (40)
c	2-CH_3	5.0	1.67 (54)	0.90 (23)
d	4-F	5.0	1.32 (43)	0.50 (13)
e	4-C_2H_5	5.0	1.90 (60)	0.95 (24)

steric (molar refractivity, MR) electronic (Field $\mathcal{F}$, Resonance $\mathcal{R}$, Hammett's constant σ and group dipole moment μ) as independent and antithrombotic activity data [percent protection (%P) at 0.5 mM dose converted to log (P/100−P)] as dependent parameters. The values of the physicochemical parameters used were taken from the literature,[18,19] and multiparameter linear regression analysis was carried out on PC-486 model using in house built program GW BASIC and/or SYSTAT (version 7.0) software.[20] Different physicochemical parameters such as hydrophobicity (πR_1, πR_2), steric (MRR_1, MRR_2) and electronic ($\mathcal{R}R_1$, $\mathcal{R}R_2$, $\mathcal{F}R_1$,



Scheme 1. (i) Dry acetone, 5 °C; (ii) (a) NaOH; (b) HCl; (c) NH_4OH; (iii) NH_4SCN, HCl, Δ; (iv) (a)$Br(CH_2)_2NH_2 \cdot HBr$, EtOH, reflux; (b) NH_4OH; (v) dry acetone or THF, Et_3N, 30 °C.



Scheme 2. Plausable intramolecular concerted mechanism for the formation of the byproducts (**3′a–e**).

$\mathcal{F}R_2$, σR_1, σR_2, μR_1, μR_2) where R_1 and R_2 indicates substituent(s) in the phenyl and phenyl carbonyl rings, respectively, were correlated as an independent parameters with log[P/100−P] as dependent variable (Table 3). In the case of disubstituent, the values were computed by simple algebraic addition of substituent coefficients for the variables π, MR, $\mathcal{R}$, $\mathcal{F}$, and σ, while in the case of μ the resultant value was obtained by vector addition of the corresponding substituents and considering their coefficient sign for final value, for example in the case of compound **29**, there are two substituent Cl and NO_2 on the phenyl group at *para* (4) and *meta* (3) positions, respectively. Their resultant μR_1 value is computed as follows:

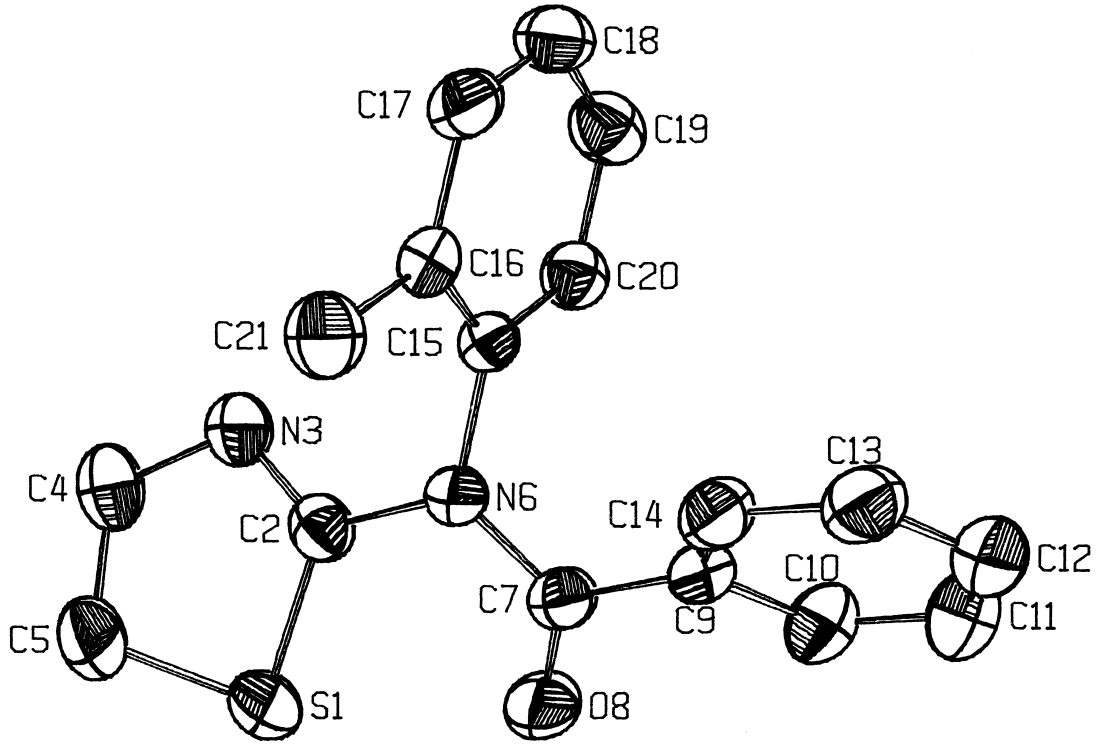


Figure 1. X-ray structure of compound 9 (ORTEP plot). Arbitrary numbering.

Table 2. Physicochemical data of 2-(*N*-aryl-*N*-aroyl)amino-4,5-dihydrothiazoles (**5**–**29**)

Compd no.	Molecular formula	R_1	R_2	Molecular weight	mp °C	%(Protection) P at 0.5 mM/kg	Log (P/100−P)
5	$C_{17}H_{13}N_2OSF_3$	2-CF_3	H	350	98–99	30	−0.3679
6	$C_{16}H_{13}N_2OSF$	4-F	H	300	101–02	37.5	−0.2218
7	$C_{18}H_{18}N_2O_3S$	2,5$(OCH_3)_2$	H	342	116–17	30	−0.3679
8	$C_{17}H_{15}N_2OSCl$	2-Cl, 6-CH_3	H	330.5	120–21	30	−0.3679
9	$C_{17}H_{16}N_2OS$	2-CH_3	H	296	100–01	20	−0.6020
10	$C_{18}H_{15}N_2O_2SF_3$	2-CF_3	4-OCH_3	380	136–38	30	−0.3679
11	$C_{18}H_{18}N_2O_2S$	2-CH_3	4-OCH_3	326	120	30	−0.3679
12	$C_{19}H_{20}N_2O_4S$	2,5$(OCH_3)_2$	4-OCH_3	372	130	40	−0.1760
13	$C_{17}H_{15}N_2O_2SF$	4-F	4-OCH_3	330	76	40	−0.1760
14	$C_{18}H_{17}N_2OSCl$	2-Cl, 6-CH_3	2-CH_3	344.5	81	25	−0.4771
15	$C_{18}H_{15}N_2OSF_3$	2-CF_3	2-CH_3	364	130–31	37.5	−0.2218
16	$C_{17}H_{15}N_2OSF$	4-F	2-CH_3	314	83–84	30	−0.3679
17	$C_{18}H_{18}N_2O_2S$	4-OCH_3	2-CH_3	326	86–87	25	−0.4771
18	$C_{18}H_{17}N_2OSCl$	4-C_2H_5	4-Cl	344.5	115	40	−0.1760
19	$C_{17}H_{14}N_2OSCl_2$	2-Cl, 6-CH_3	4-Cl	365	115	33.3	−0.3011
20	$C_{16}H_{12}N_2SOFCl$	4-F	4-Cl	334.5	105	33.3	−0.3017
21	$C_{17}H_{15}N_2OSBr$	2-CH_3	2-Br	375	98	30	−0.3679
22	$C_{16}H_{13}N_2OSBr$	H	2-Br	361	166	40	−0.1760
23	$C_{17}H_{14}N_2OSBrCl$	2-Cl, 6-CH_3	2-Br	409.5	118	37.5	−0.2218
24	$C_{18}H_{17}N_2O_5S$	2,5$(OCH_3)_2$	4-NO_2	387	140	42.9	−0.1241
25	$C_{16}H_{12}N_4O_5S$	4-NO_2	4-NO_2	372	168	50.0	0.0000
26	$C_{16}H_{12}N_2O_3SF$	4-F	4-NO_2	345	93	40	−0.1760
27	$C_{17}H_{15}N_2SO_3$	2-CH_3	4-NO_2	341	98	42.1	−0.1383
28	$C_{17}H_{15}N_3SO_4$	4-OCH_3	4-NO_2	357	110	50.0	0.0000
29	$C_{16}H_{11}N_4SO_5Cl$	4-Cl, 3-NO_2	4-NO_2	406.5	166	64.7	0.2631

$$\mu R_{1=}[(\mu Cl)^2 + (\mu NO_2)^2 + 2(\mu Cl)(\mu NO_2)\cos 60^\circ]^{1/2}$$

$$= [(-1.59)^2 + (-4.13)^2 + 2(-1.59)(-4.13)(0.5)]^{1/2}$$

$$= [2.5281 + 17.0569 + 6.5667]^{1/2} = [26.1517]^{1/2}$$

$$= -5.11$$

(Note: Angle between the Cl and NO_2 is 60° and as both are electron withdrawing groups and are having negative signs before their coefficients value, overall sign is taken as negative before the final computed value.)

In the preliminary analysis by analyzing the correlation matrix (Table 4) it is observed that the antithrombotic activity, log (P/100−P) is poorly correlated ($r<0.4$) with πR_1, πR_2, MRR_1, MRR_2, $\mathcal{R}R_1$ and $\mathcal{R}R_2$; slightly correlated ($0.4<r<0.6$) $\mathcal{F}R_1$, σR_1, μR_1, and correlated ($r>0.6$) with $\mathcal{F}R_2$, σR_2, μR_2.

Considering the above and keeping in view that there is no colinearity between the two sets (σR_1, μR_1 and $\mathcal{F}R_1$) and (σR_2, μR_2 and $\mathcal{F}R_2$) of electronic parameters but they have high intercorrelation ($r>0.7$) among each other in each set, the two parameter equations with one parameter from each set at one time were deduced. None of these equations (1)–(9) had parameter with intercorrelation greater than 0.5 ($r<0.5$). All these nine two-parameter equations had high correlation coefficient ($r>0.77$) with high statistical significance >99.9% ($F_{2,22} > 15.0$; $F_{2,22\alpha:\ 0.001} = 11.0$). The observed ratio of 1:1.5 with regression coefficients of electronic parameters corresponding to R_1 and R_2 positions of molecule suggest that the electronic influence of the groups positioned in the benzoyl part (R_2) of the molecules is more on the observed antithrombotic activity compared to the corresponding electronic influence of the

Table 3. Physicochemical parameters used in generating 2D QSAR equations for 2-(*N*-aryl-*N*-aroyl)amino- 4,5-dihydrothiazoles (**5**–**29**)

Comp no.	R_1	R_2	μ -R_1	μ-R_2	σ-R_1	σ-R_2	$\mathcal{F}R_1$	$\mathcal{F}R_2$	π-R_1	π-R_2	$\mathcal{R}R_1$	$\mathcal{R}R_2$	MR-R_1	MR-R_2
5	2-CF_3	H	−2.61	0.03	0.54	0.00	0.38	0.00	0.88	0.00	0.19	0.00	5.02	1.03
6	4-F	H	−1.43	0.03	0.06	0.00	0.43	0.00	0.14	0.00	−0.34	0.00	0.92	1.03
7	2,5(OCH_3)$_2$	H	−1.30	0.03	−0.54	0.00	0.52	0.00	−0.04	0.00	−1.02	0.00	15.74	1.03
8	2-Cl, 6-CH_3	H	−1.80	0.03	0.06	0.00	0.37	0.00	1.27	0.00	−0.28	0.00	11.68	1.03
9	2-CH_3	H	0.36	0.03	−0.17	0.00	−0.04	0.00	0.56	0.00	−0.13	0.00	5.65	1.03
10	2-CF_3	4-OCH_3	−2.61	−1.30	0.54	−0.27	0.38	0.26	0.88	−0.02	0.19	−0.51	5.02	7.87
11	2-CH_3	4-OCH_3	0.36	−1.30	−0.17	−0.27	−0.04	0.26	0.56	−0.02	−0.13	−0.51	5.65	7.87
12	2,5(OCH_3)$_2$	4-OCH_3	−1.30	−1.30	−0.54	−0.27	0.52	0.26	−0.04	−0.02	−1.02	−0.51	15.74	7.87
13	4-F	4-OCH_3	−1.43	−1.30	0.06	−0.27	0.43	0.26	−0.02	−0.02	−0.34	−0.51	0.92	7.87
14	2-Cl, 6-CH_3	2-CH_3	−1.80	0.36	0.06	−0.17	0.37	−0.04	1.27	0.56	−0.28	−0.13	11.68	5.65
15	2-CF_3	2-CH_3	−2.61	0.36	0.54	−0.17	0.38	−0.04	0.88	0.56	0.19	−0.13	5.02	5.65
16	4-F	2-CH_3	−1.43	0.36	0.06	−0.17	0.43	−0.04	0.14	0.56	−0.34	−0.13	0.92	5.65
17	4-OCH_3	2-CH_3	−1.30	0.36	−0.27	−0.17	0.26	−0.04	−0.02	0.56	−0.51	−0.13	7.87	5.65
18	4-C_2H_5	4-Cl	0.39	−1.59	−0.15	0.23	−0.05	0.41	1.02	0.71	−0.10	−0.15	10.30	6.03
19	2-Cl, 6-CH_3	4-Cl	−1.80	−1.59	0.06	0.23	0.37	0.41	0.14	0.71	−0.28	−0.15	11.68	6.03
20	4-F	4-Cl	−1.43	−1.59	0.06	0.23	0.43	0.41	1.27	0.71	−0.34	−0.15	0.92	6.03
21	2-CH_3	2-Br	0.36	−1.57	−0.17	0.23	0.04	0.44	0.56	0.86	−0.13	−0.17	5.65	8.88
22	H	2-Br	0.03	−1.57	0.00	0.23	0.00	0.44	0.00	0.86	0.00	−0.17	1.03	8.88
23	2-Cl, 6-CH_3	2-Br	−1.80	−1.57	0.06	0.23	0.37	0.44	1.27	0.86	−0.28	−0.17	11.68	8.88
24	2,5(OCH_3)$_2$	4-NO_2	−1.30	−4.13	−0.54	0.78	0.52	0.67	−0.04	−0.28	−1.02	0.16	15.74	7.36
25	4-NO_2	4-NO_2	−4.13	−4.13	0.78	0.78	0.67	0.67	−0.28	−0.28	0.16	0.16	7.36	7.36
26	4-F	4-NO_2	−1.43	−4.13	0.06	0.78	0.43	0.67	0.14	−0.28	−0.34	0.16	0.92	7.36
27	2-CH_3	4-NO_2	0.36	−4.13	−0.17	0.78	−0.04	0.67	0.56	−0.28	−0.13	0.16	5.65	7.36
28	2-OCH_3	4-NO_2	−1.30	−4.13	−0.27	0.78	0.26	0.67	−0.02	−0.28	−0.51	0.16	7.87	7.36
29	4-Cl, 3-NO_2	4-NO_2	−5.11	−4.13	1.01	0.78	1.08	0.67	0.43	−0.28	0.01	0.16	13.39	7.36

Table 4. Correlation matrix of the parameters used in 2-D QSAR study

	σR_1	σR_2	πR_1	πR_2	MRR_1	MRR_2	$\mathcal{F}R_1$	$\mathcal{F}R_2$	$\mathcal{R}R_1$	$\mathcal{R}R_2$	μR_1	μR_2	Log(P/100−P)
σR_1	1.000												
σR_2	0.131	1.000											
πR_1	0.125	−0.260	1.000										
πR_2	−0.197	−0.371	0.370	1.000									
MRR_1	−0.059	0.125	0.199	−0.130	1.000								
MRR_2	0.123	0.083	−0.025	0.278	−0.053	1.000							
$\mathcal{F}R_1$	0.647	0.199	−0.212	−0.357	0.310	−0.010	1.000						
$\mathcal{F}R_2$	0.083	0.847	−0.253	−0.273	0.085	0.462	0.107	1.000					
$\mathcal{R}R_1$	0.610	−0.003	0.411	0.156	−0.494	0.137	−0.167	0.008	1.000				
$\mathcal{R}R_2$	0.208	0.708	−0.108	−0.268	0.118	−0.270	0.252	0.259	0.031	1.000			
μR_1	−0.860	−0.181	0.010	0.287	−0.202	0.014	−0.900	−0.078	−0.217	−0.242	1.000		
μR_2	−0.136	−0.885	0.328	0.482	−0.109	−0.349	−0.205	−0.968	0.027	−0.351	0.168	1.000	
Log(P/100−P)	0.422	0.681	−0.315	−0.381	0.148	0.254	0.514	0.734	0.038	0.271	−0.476	−0.768	1.000

substituent present in aryl part (R_1) of the the molecules. The positive value of Hammett's constant (σ) at both positions R_1 and R_2 suggest that electronic influence is more than steric and hydrophobic factor and presence of electron withdrawing groups at these positions will increase activity. Since the σ parameter takes into account the electronic influence in terms of resonance ($\mathcal{R}$) and field effect ($\mathcal{F}$) described by Swain and Lupton, hence the better correlation with field effect ($\mathcal{F}$), both at R_1 and R_2 position indicate that the electronic influence here is primarily governed by the field effect [eq (5)] over others [eqs (2), (4), (6) and (8)] with higher correlation coefficient value ($r=0.86$) of high statistical significance $>99.9\%$ ($F_{2,22}=29.9$; $F_{2,22\alpha:0.001}=11.0$) as that of eq 5.

$$\text{Log}\,(P/100-P)=0.186(\pm0.077)\sigma R_1+0.294(\pm0.064)\sigma R_2-0.317$$
$$n=25\quad r=0.759\quad s=0.122\quad F=15.00 \tag{1}$$

$$\text{Log}\,(P/100-P)=0.199(\pm0.067)\sigma R_1+0.458(\pm0.080)\mathcal{F}R_2-0.404$$
$$n=25\quad r=0.819\quad s=0.108\quad F=22.41 \tag{2}$$

$$\text{Log}\,(P/100-P)=0.178(\pm0.065)\sigma R_1-0.078(\pm0.013)\mu R_2-0.384$$
$$n=25\quad r=0.832\quad s=0.104\quad F=24.78 \tag{3}$$

$$\text{Log}\,(P/100-P)=0.078(\pm0.093)\mathcal{F}R_1+0.278(\pm0.063)\sigma P2-0.389$$
$$n=25\quad r=0.783\quad s=0.117\quad F=17.41 \tag{4}$$

$$\text{Log}\,(P/100-P)=0.301(\pm0.076)\mathcal{F}R_1+0.447(\pm0.072)\mathcal{F}R_2-0.485$$
$$n=25\quad r=0.855\quad s=0.097\quad F=29.88 \tag{5}$$

$$\text{Log}\,(P/100-P)=0.254(\pm0.079)\mathcal{F}R_1-0.074(\pm0.012)\mu R_2-0.449$$
$$n=25\quad r=0.850\quad s=0.099\quad F=28.56 \tag{6}$$

$$\text{Log}\,(P/100-P)=-0.048(\pm0.018)\mu R_1+0.284(\pm0.064)\sigma R_2-0.370$$
$$n=25\quad r=0.770\quad s=0.120\quad F=16.00 \tag{7}$$

$$\text{Log}\,(P/100-P)=-0.056(\pm0.015)\mu R_1+0.456(\pm0.074)\mathcal{F}R_2-0.468$$
$$n=25\quad r=0.846\quad s=0.100\quad F=27.71 \tag{8}$$

$$\text{Log}\,(P/100-P)=-0.047(\pm0.015)\mu R_1-0.076(\pm0.012)\mu R_2-0.435$$
$$n=25\quad r=0.845\quad s=0.101\quad F=27.40 \tag{9}$$

The 2-D QSAR results are suggesting that it is only the electronic factors, namely Hammett constant (σ), group dipole moment (μ) and field effect ($\mathcal{F}$) that are crucial for the antithrombotic activity in the present set of dihydrothiazoles (**5**–**29**) and steric/bulk and hydrophobic factors have got no influence for the activity and are not playing any important role here.

The above results also indicate that dihydrothiazoles may be considered as a good pharmacophore for the antithrombotic activity and antithrombotic activity in this series is negatively influenced by the electronic parameter in terms of group dipole moment (μ), field effect ($\mathcal{F}$) and Hammett's field constant (σ) of the substituents present in the phenyl and benzoyl rings in the ratio of approximately 1:1.5. This altogether means the same thing that the increase in the positive character at 2-amino position of the title compounds positively contribute for the activity and may be involved in electrostatic interactions or in the binding with the anionic site. Further antithrombotic activity can be increased by polysubstituting the phenyl and benzoyl rings with groups having highly negatively μ values and highly positive $\mathcal{F}$ and σ values, namely NO_2, CN, CO_2H, $CONH_2$, CONHR, SO_2F, SO_2OR, NR_3^+, N_2^+, etc.

The reliability of the equations obtained by multiple regression analysis is reflected by the similarities in antithrombotic activity observed in vivo testing and calculated by these equations for the substituted dihydrothiazoles (**5**–**29**) (Table 5).

Table 5. Comparision between the observed and calculated antithrombotic activity from the 2-D QSAR equations having $r>0.80$

Compd no.	Observed	Calculated					
		eq (2)	eq (3)	eq (5)	eq (6)	eq (8)	eq (9)
5	−0.3679	−0.296	−0.290	−0.371	−0.354	−0.322	−0.313
6	−0.2218	−0.392	−0.376	−0.356	−0.342	−0.388	−0.369
7	−0.3679	−0.434	−0.413	−0.328	−0.319	−0.395	−0.375
8	−0.3679	−0.392	−0.376	−0.374	−0.357	−0.367	−0.351
9	−0.6020	−0.438	−0.416	−0.497	−0.461	−0.488	−0.454
10	−0.3679	−0.177	−0.187	−0.254	−0.256	−0.203	−0.212
11	−0.3679	−0.319	−0.313	−0.381	−0.363	−0.370	−0.353
12	−0.1760	−0.315	−0.309	−0.212	−0.220	−0.277	−0.274
13	−0.1760	−0.273	−0.272	−0.290	−0.243	−0.269	−0.274
14	−0.4771	−0.411	−0.401	−0.391	−0.387	−0.385	−0.376
15	−0.2218	−0.315	−0.316	−0.388	−0.379	−0.340	−0.338
16	−0.3679	−0.411	−0.401	−0.373	−0.366	−0.406	−0.394
17	−0.4771	−0.476	−0.460	−0.425	−0.410	−0.413	−0.400
18	−0.1760	−0.246	−0.287	−0.137	−0.344	−0.303	−0.332
19	−0.3011	−0.204	−0.249	−0.172	−0.237	−0.180	−0.246
20	−0.3017	−0.204	−0.249	−0.190	−0.222	−0.201	−0.228
21	−0.3679	−0.237	−0.292	−0.300	−0.343	−0.287	−0.332
22	−0.1760	−0.203	−0.262	−0.288	−0.332	−0.269	−0.316
23	−0.2218	−0.191	−0.251	−0.177	−0.238	−0.166	−0.230
24	−0.1241	−0.127	−0.089	−0.029	−0.010	−0.090	−0.059
25	0.0000	−0.058	0.076	0.015	0.028	0.069	0.075
26	−0.1760	−0.085	−0.052	−0.056	−0.033	−0.082	−0.052
27	−0.1383	−0.131	−0.094	−0.198	−0.152	−0.183	−0.137
28	0.0000	−0.154	−0.110	−0.107	−0.076	−0.089	−0.059
29	0.2631	0.090	0.105	0.139	0.132	0.124	0.121

Experimental

Preparation of *N*-phenyl-*N'*-benzoylthiourea (2a)

A solution of benzoyl isothiocyanate (1.63 g, 0.01 mol) in dry acetone (20 mL) was added dropwise to a stirred solution of aniline **1a** (0.93 g, 0.01 mol) in dry acetone (30 mL) at 20 °C over 10 min. After stirring the mixture at 20 °C for 2 h, it was concentrated, filtered, washed with a small amount of cold dry acetone and dried to give **2a**. Yield 2.4 g (94%): MP 145–146 °C (lit.[13] MP 147.5–148.5 °C).

Similarly, other compounds (**2b**–**j**) of this series were prepared from corresponding substituted anilines.

General method for the preparation of *N*-arylthioureas

Method A: preparation of *N*-phenylthiourea (3a, R_1 = H). 2a (1.28 g, 5.0 mmol) was added in one portion to a stirring 5% aqueous NaOH (20 mL) solution at 90 °C and stirring was continued for further 20 min. The hot reaction mixture was filtered to get byproduct **3'a** and the filtrate obtained was cooled, acidified with 15% aqueous HCl and its pH was adjusted to ~8.0 with aqueous ammonia to remove benzoic acid. The solid obtained was filtered, washed with water and dried to give **3a**.

Yield 0.55 g (73%): mp 152–153 °C (lit.[13] mp 154.5–155.5 °C)

Method B: preparation of *N*-(4-chloro-3-nitrophenyl)-thiourea (3j, R_1 = 4-Cl, 3-NO_2). A saturated solution of ammonium thiocyanate (0.76 g, 0.01 m) was added to a clear solution of 4-chloro-3-nitroaniline **1j** (1.72 g, 0.01 m) in 15% aqueous HCl (2.06 mL, 0.01 m), and the resultant solution was boiled until a viscous layer or turbidity appeared (≈2 h). It was then poured into crushed ice and the precipitated product **3j** was filtered, washed with water, dried and used for next step without further purification.

Yield 1.75 g (76%): mp 185–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 2.70 (brs, 2H, NH_2), 7.46 (d, J = 8.7 Hz, 1H, ArH), 7.87 (dd, J = 2.3, 8.7 Hz, 1H, ArH), 8.34 (d, J = 2.4 Hz, 1H, ArH), 9.86 (brs, 1H, NH); FTIR (KBr, cm^{-1}): 702, 824, 1043, 1258, 1319, 1352, 1460, 1529, 1582, 1608, 3003, 3069, 3125, 3169, 3275, 3433; MS (EI): m/z 231 (M^+). Anal. calcd for $C_7H_6N_3O_2SCl$: C 22.17; H 1.60; N 11.08%. Found: C 22.10; H 1.44; N 11.00%.

The other *N*-arylthioureas (**3a**–**i**) of the series were prepared adopting either of the above procedures.

Preparation of 2-(4-chloro-3-nitrophenyl)amino-4,5-dihydrothiazole (4j, R_1 = 4-Cl, 3-NO_2). A solution of 2-bromoethylamine hydrobromide (2.05 g, 0.01 m) in 5.0 mL of water was added to a solution of **3j** (2.31 g, 0.01 m) in ethanol (40 mL), and the reaction mixture was refluxed under stirring overnight. Ethanol was distilled off under reduced pressure and the reaction mixture was basified with dilute aqueous ammonia solution. The product **4j** was filtered, washed with water, dried and recrystallised with methanol.

Yield = 2.20 g (60%); mp = 150 °C; EIMS (m/z) = 257.5 (m^+); ^{1}H NMR ($CDCl_3$) (400 MHz) = δ 3.37 (t, J = 7.0 Hz, 2H, SCH_2), 3.74 (t, J = 7.0 Hz, 2H, NCH_2), 7.15 (dd, J = 3.0, 9.0 Hz, 1H, ArH), 7.42 (d, J = 9.0 Hz, IH, ArH), 7.58 (d, J = 3.0 Hz, 1H, ArH); FTIR (KBr) = 689, 822, 887, 1065, 1126, 1211, 1269, 1348, 1475, 1524, 1626, 2363. Anal. calcd for $C_9H_8N_3O_2SCl$: C 41.95; H 3.13; N 16.3%. Found: C 41.81; H 3.08; N 16.14%.

Preparation of *N*-(4-chloro-3-nitrophenyl)-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-4-nitrobenzamide (29, R_1 = 4-Cl, 3-NO_2). 4-Nitrobenzoyl chloride (0.40 g, 2.2 mmol) and dry triethylamine (0.30 mL, 2.2 mmol) were added to a solution of (**4j**) (0.52 g, 2.0 mmol) in dry acetone (15 mL), and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then concentrated in vacuo and water was added to get the crude product (**29**). It was filtered, washed with water, dried and recrystallised with methanol.

Yield 0.65 g (80%): mp 166 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (t, J = 6.8 Hz, 2H, SCH_2), 4.37 (t, J = 6.8 Hz, 2H, NCH_2), 7.02 (dd, J = 2.6, 8.6 Hz, 1H, ArH), 7.32 (d, J = 2.4 Hz, 1H, ArH), 7.54 (d, J = 6.8 Hz, 1H, ArH), 7.97 (d, J = 9.0 Hz, 2H, ArH), 8.30 (d, J = 9.0 Hz, 2H, ArH); FTIR (KBr, cm^{-1}): 708, 857, 1015, 1161, 1358, 1474, 1531, 1599, 1638, 3082; MS(EI): m/z 406 (M^+). Anal. calcd for $C_{16}H_{11}N_4O_5SCl$: C 47.24; H 2.73%. Found: C 47.18; H 2.78%.

Similarly, other compounds (**5**–**28**) of the series were prepared and their physicochemical data is given below.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-trifluoromethylphenyl)benzamide(5, R_1 = 2-CF_3, R_2 = H).** Yield 68%: mp 98–99 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.20 (t, J = 8.0 Hz, 2H, SCH_2), 4.20 (t, J = 8.0 Hz, 2H, NCH_2), 7.00–7.80 (m, 9H, ArH); IR (KBr, cm^{-1}): 1050, 1140, 1180, 1280, 1330, 1620, 1650, 1690; MS(EI): m/z 350 (M^+). Anal. calcd for $C_{17}H_{13}N_2OSF_3$: C 58.23; H 3.74%; N 8.0. Found: C 58.13; H 3.62; N 7.84%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-fluorophenyl)benzamide (6, R_1 = 4-F, R_2 = H).** Yield 78%: mp 101–102 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.25 (t, J = 8.0 Hz, 2H, SCH_2), 3.90 (t, J = 8.0 Hz, 2H, NCH_2), 6.80–7.40 (m, 9H, ArH); IR (KBr, cm^{-1}): 1020, 1220, 1300, 1500, 1600, 1620; MS(EI): m/z 300 (M^+). Anal. calcd for $C_{16}H_{13}N_2OSF$: C 63.98; H 4.36; N 9.33%. Found: C 63.84; H 4.30; N 9.28%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(2,5-dimethoxyphenyl)benzamide (7, R_1 = 2,5(OCH_3)$_2$, R_2 = H).** Yield 72%: mp 116–117 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.20 (t, J = 8.0 Hz, 2H, SCH_2), 3.70 (s, 6H, OCH_3), 4.30 (t, J = 8.0 Hz, 2H, NCH_2), 6.30 (d, J = 3.0 Hz, 1H, ArH), 6.60 (d, J = 3.0 Hz, 1H, ArH), 6.70 (s, 1H, ArH), 7.30–7.50 (m, 3H, ArH), 7.70–7.90 (m, 2H, ArH); FTIR (KBr, cm^{-1}): 1030, 1050, 1130, 1170, 1340, 1650, 3000;

MS (EI): m/z 342 (M^+). Anal. calcd for $C_{18}H_{18}N_2O_3S$: C 63.02; H 5.20; N 8.22%. Found: C 63.20; H 5.28; N 8.15%.

***N*-(2-Chloro-6-methylphenyl)-*N*-(4,5-dihydro-1,3-thiazol-2-yl)benzamide (8, R_1 = 2-Cl, 6-CH_3, R_2 = H).** Yield 66%: mp 120–121 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3), 3.20–3.50 (m, 2H, SCH_2), 3.90–4.15 (m, 1H, NCH_2), 4.25–4.45 (m, 1H, NCH_2), 6.90–7.90 (m, 8H, Ar); IR (KBr, cm^{-1}): 1040, 1180, 1310, 1460, 1630, 1660; MS(EI): m/z 330.5 (M^+). Anal. calcd for $C_{17}H_{15}N_2OSCl$: C 61.72; H 4.57; N 8.47%. Found: C 61.58; H 4.36; N 8.39%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(2-methylphenyl)benzamide (9, R_1 = CH_3, R_2 = H).** Yield 76%: mp 100–101 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H, CH_3), 3.00–3.00 (m, 2H, SCH_2), 3.70–4.20 (m, 2H, NCH_2), 6.70–7.50 (m, 9H, ArH); IR (KBr, cm^{-1}): 1020, 1170, 1300, 1330, 1610, 1660; MS (EI): m/z 296 (M^+). Anal. calcd for $C_{17}H_{16}N_2OS$: C 68.89; H 5.44; N 9.45%. Found: C 68.80, H 5.40; N 9.38%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-4-methoxy-*N*-(2-trifluoromethylphenyl)benzamide (10, R_1 = 2-CF_3, R_2 = 4-OCH_3).** Yield 80%: mp 136–138 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.20 (t, J = 8.0 Hz, SCH_2), 3.70 (s, 3H, OCH_3), 4.20 (t, J = 8.0 Hz, 2H, NCH_2), 6.70–7.60 (m, 8H, ArH); IR (KBr, cm^{-1}): 1030, 1160, 1350, 1530, 1600, 1600, 1660, 2950; MS(EI): m/z 380 (M^+). Anal. calcd for $C_{18}H_{15}N_2O_2SF_3$: C 56.84; H 3.97; N 7.36%. Found: C 56.68, H 3.92; N 7.26%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-4-methoxy-*N*-(2-methoxyphenyl)benzamide(11, R_1 = 2-CH_3, R_2 = 4-OCH_3).** Yield 79%: mp 120 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.90 (s, 3H, CH_3), 3.10 (t, J = 8.0 Hz, 2H, SCH_2), 3.70 (s, 3H, OCH_3), 4.10 (t, J = 8.0 Hz, 2H, NCH_2), 6.50–7.10 (m, 8H, ArH); IR (KBr, cm^{-1}): 1015, 1161, 1358, 1474, 1531, 1599, 1680, 2950; MS(EI): m/z 326 (M^+). Anal. calcd for $C_{18}H_{18}N_2O_2S$: C 66.23; H 5.56; N 8.58%. Found: C 66.14; H 5.50; N 8.52%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(2,5-dimethoxyphenyl)-4-methoxybenzamide (12, R_1 = 2,5-$(OCH_3)_2$, R_2 = 4-OCH_3).** Yield 77%: mp 130 °C; ^{1}H NMR (90 MHz, CD_3COCD_3): δ 3.20 (t, J = 8.0 Hz, 2H, SCH_2), 3.75 (s, 6H, $(OCH_3)_2$), 3.80 (s, 3H, OCH_3), 4.20 (t, J = 8.0 Hz, 2H, NCH_2), 6.20–6.80 (m, 4H, ArH), 7.15–7.30 (m, 1H, ArH), 7.70 (d, J = 9.0 Hz, 2H, ArH); IR (KBr, cm^{-1}): 1040, 1260, 1340, 1510, 1600, 1620, 3000; MS (EI): m/z 372 (M^+). Anal. calcd for $C_{19}H_{20}N_2O_4S$: C 61.27; H 5.41%. Found: C 61.15, H 5.28%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-fluorophenyl)-4-methoxybenzamide (13, R_1 = 4-F, R_2 = 4-OCH_3).** Yield 72%: mp 76 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.15 (t, J = 8.0 Hz, 2H, SCH_2), 3.70 (s, 3H, OCH_3), 4.10 (t, J = 8.0 Hz, 2H, NCH_2), 6.50–6.90 (m, 6H, ArH), 7.6 (d, J = 9.0 Hz, 2H, ArH); IR (KBr, cm^{-1}): 1030, 1170, 1300, 1500, 1640; MS (EI): m/z 330 (M^+). Anal. calcd for $C_{17}H_{15}N_2O_2$ FS: C 61.80; H 4.58; N 8.48%. Found: C 61.74; H 4.50; N 8.42%.

***N*-(2-Chloro-6-methylphenyl)-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-2-methylbenzamide (14, R_1 = 2-Cl, 6-CH_3, R_2 = 2-CH_3).** Yield 68%: mp 81 °C; ^{1}H NMR (90 MHz, $CDCl_3$); δ 1.80 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.15 (t, J = 8.0 Hz, 2H, SCH_2), 4.30 (t, J = 8.0 Hz, 2H, NCH_2), 6.70–7.30 (m, 7H, ArH); IR (KBr, cm^{-1}): 1150, 1300, 1440, 1640, 2940; MS(EI): m/z 344 (M^+). Anal. calcd for $C_{18}H_{17}N_2OSCl$: C 62.69; H 4.97; N 8.12. Found: C 62.60, H 4.86; N 8.06.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-2-methyl-*N*-(2-trifluoromethylphenyl)benzamide (15, R_1 = 2-CF_3, R_2 = 2-CH_3).** Yield 82%: mp 130–131 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.4 (s, 3H, CH_3), 3.25 (t, J = 8.0 Hz, 2H, SCH_2), 4.40 (t, J = 8.0 Hz, 2H, NCH_2), 6.70–7.70 (m, 8H, ArH); IR (KBr, cm^{-1}): 1120, 1320, 1460, 1640; MS (EI): m/z 364 (M^+). Anal. calcd for $C_{18}H_{15}N_2OSF_3$: C 59.33; H 4.15; N 7.69%. Found: C 59.36; H 4.20; N 7.81%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-fluorophenyl)-2-methylbenzamide (16, R_1 = 4-F, R_2 = 2-CH_3).** Yield 81%: mp 83–84 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.25 (t, J = 8.0 Hz, 2H, SCH_2), 3.90 (t, J = 8.0 Hz, 2H, NCH_2), 6.70–7.20 (m, 8H, ArH); FTIR (KBr, cm^{-1}): 1040, 1240, 1300, 1520, 1620, 1620, 1700; MS(EI): m/z 314 (M^+). Anal. calcd for $C_{17}H_{15}N_2OSF$: C 64.95; H 4.81; N 8.91%. Found: C 64.91; H 4.76; N 8.84%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-methoxyphenyl)-2-methylbenamide (17, R_1 = 4-OCH_3, R_2 = 2-CH_3).** Yield 82%: mp 86–87 °C; ^{1}H NMR (90 MHz, $CDCl_3$) = δ 2.30 (s, 3H, CH_3), 3.15 (t, J = 8.0 Hz, 2H, SCH_2) 3.65 (s, 3H, OCH_3), 4.20 (t, J = 8.0 Hz, 2H, NCH_2), 6.30–6.70 (m, 4H, ArH), 7.00–7.20 (m, 4H, ArH); IR (KBr, cm^{-1}): 1060, 1180, 1260, 1360, 1520, 1670; MS(EI): m/z 326 (M^+). Anal. calcd for $C_{18}H_{18}O_2S$: C 66.23; H 5.56; N 8.58%. Found: C 62.16; H 5.48; N 8.48%.

4-Chloro-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-*N*-(4-ethylphenyl)benzamide (18, R_1 = 4-C_2H_5, R_2 = 4-Cl). Yield 76%: mp 115 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.10 (t, J = 9.0 Hz, 3H, CH_3), 2.55 (q, J = 8.0 Hz, 2H, CH_2), 3.20 (t, J = 9.0 Hz, 2H, SCH_2), 3.85 (t, J = 9.0 Hz, 2H, NCH_2), 6.90–7.40 (m, 8H, ArH); IR (KBr, cm^{-1}): 1000, 1240, 1450, 1590, 1670, 2960; MS(EI): m/z 344 (M^+). Anal. calcd for $C_{18}H_{17}N_2OSCI$: C 62.69; H 4.97; N 8.12%. Found: C 62.89; H 4.87; N 8.21%.

4-Chloro-*N*-(2-chloro-6-methylphenyl)-*N*-(4,5-dihydro-1,3-thiazol-2-yl)benzamide (19, R_1 = 2-Cl, 6-CH_3, R_2 = 4-Cl). Yield 72%: mp 115 °C; ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.00 (s, 3H, CH_3), 3.20 (t, J = 8.0 Hz, 2H, SCH_2), 4.25 (t, J = 8.0 Hz, 2H, NCH_2), 6.70–7.40 (m, 7H, ArH); IR (KBr, cm^{-1}): 1000, 1160, 1320, 1400, 1600, 1670, 2920, 2980, 3080; MS(EI): m/z 365 (M^+). Anal. cacld for $C_{17}H_{14}N_2OSCl_2$: C 55.90; H 3.86; N 7.67%. Found: C 56.0; H 3.90; N 7.72%.

2-Bromo-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-*N*-(4-fluorophenyl)benzamide (20, R_1 = 4-F, R_2 = 2-Cl). Yield 68%: mp 105 °C; ^{1}H NMR (90 MHz, $CDCl_3$): δ 3.20 (t,

$J = 8.0$ Hz, 2H, SCH_2), 4.30 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.70–7.50 (m, 8H, ArH); IR (KBr, cm^{-1}) = 1000, 1100, 1320, 1440, 1590, 1630, 2860, 3060, 3450; MS(EI): m/z 334.5(M^+).

2-Bromo-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-*N*-(2-methylphenyl)benzamide (21, $R_1 = 2\text{-}CH_3$, $R_2 = 2\text{-}Br$). Yield 70%: mp 98 °C ; ^1H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H, CH_3), 3.30 (t, $J = 8.0$ Hz, 2H, SCH_2), 4.30 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.60–7.60 (m, 8H, ArH); IR (KBr, cm^{-1}): 1010, 1120, 1330, 1440, 1530, 1590, 1650, 2880, 3060; MS(EI): m/z 375(M^+). Anal. cacld for $C_{17}H_{15}N_2OSBr$: C 54.41; H 4.03; N 7.46%. Found: C 54.31; H 4.00; N 7.52%.

2-Bromo-*N*-(4,5-dihydro-1,3-thiazol-2-yl)-*N*-phenylbenzamide (22, $R_1 = H$, $R_2 = 2\text{-}Br$). Yield 73%: mp 166 °C; ^1H NMR (90 MHz, $CDCl_3$): δ 3.25 (t, $J = 8.0$ Hz, 2H, SCH_2), 4.35 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.95–7.50 (m, 9H, ArH); IR (KBr, cm^{-1}) 1010, 1330, 1490, 1600, 1640, 2920, 3000; MS(EI): m/z 361(M^+).

2-Bromo-*N*-(2-chloro-6-methylphenyl)-*N*-(4,5-dihydro-1,3-thiazol-2-yl)benzamide (23, $R_1 = 2\text{-}Cl$, $6\text{-}CH_3$, $R_2 = 2\text{-}Br$). Yield 72%: mp 118 °C; ^1H NMR (60 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 3.10–3.40 (m, 2H, SCH_2), 3.80–4.10 (m, 2H, NCH_2), 6.70–7.30 (m, 7H, ArH); IR (KBr, cm^{-1}): 1020, 1280, 1330, 1600, 1670, 2860, 2940, 3080; MS(EI): m/z 409.5(M^+).

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(2,5-dimethoxyphenyl)-4-nitrobenzamide (24, $R_1 = 2,5\text{-}(OCH_3)_2$, $R_2 = 4\text{-}NO_2$).** Yield 76%: mp 140 °C ; ^1H NMR (300 MHz, $CDCl_3$): δ 3.25 (t, $J = 8.0$ Hz, 2H, SCH_2), 3.62 (s, 3H, OCH_3) 3.66 (s, 3H, OCH_3) 3.90 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.60–6.80 (m, 3H, ArH), 7.50 (d, $J = 9.0$ Hz, 2H, ArH), 8.00 (d, $J = 9.0$ Hz, 2H, ArH); FTIR (KBr, cm^{-1}): 1010, 1210, 1300, 1500, 1600, 1670, 2900, 2980; MS(EI): m/z 397 (M^+). Anal. calcd for $C_{18}H_{17}N_2O_5S$: C 55.81; H 4.42; N 10.85%. Found: C 55.68; H 4.36; N 10.68%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-4-nitro-*N*-(4-nitrophenyl)benzamide (25, $R_1 = 4\text{-}NO_2$, $R_2 = 4\text{-}NO_2$).** Yield 77%: mp 168 °C; ^1H NMR (300 MHz, $CDCl_3$); δ 3.30 (t, $J = 8.0$ Hz, 2H, SCH_2), 4.37 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.70 (d, $J = 9.0$ Hz, 1H, ArH,), 6.90–7.50 (m, 3H, ArH), 7.65 (d, $J = 9.0$ Hz, 2H, ArH,), 8.10 (d, $J = 9.0$ Hz, 2H, ArH); IR (KBr, cm^{-1}): 830, 1100, 1150, 1300, 1440, 1520, 1630; MS(EI): m/z 372 (M^+). Anal. calcd for $C_{16}H_{12}N_4O_5S$: C 51.61; H 3.25; N 15.05%. Found: C 51.71, H 3.21; N 15.0%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(4-fluorophenyl)-4-nitrobenzamide (26, $R_1 = 4\text{-}F$, $R_2 = 4\text{-}NO_2$).** Yield 71%: MP 93 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.30 (t, $J = 8.0$ Hz, 2H, SCH_2), 4.25 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.40–7.25 (m, 4H, ArH), 7.61 (d, $J = 9.0$ Hz, 2H, ArH), 8.10 (t, $J = 9.0$ Hz, 2H, ArH); IR (KBr, cm^{-1}): 1090, 1190, 1270, 1340, 1430, 1440, 1500, 1530, 1530, 1630, 1720, 2860, 3080, 3120, MS (EI): m/z 345 (M^+). Anal. calcd for $C_{16}H_{12}N_2O_3SF$: C 51.13; H 3.22; N 11.18%. Found: C 51.10; H 3.20; N 11.15%.

***N*-(4,5-Dihydro-1,3-thiazol-2-yl)-*N*-(2-methylphenyl)-4-nitrobenzamide (27, $R_1 = 2\text{-}CH_3$, $R_2 = 4\text{-}NO_2$).** Yield 70%: MP 98 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H, CH_3), 3.30 (t, $J = 8.0$ Hz, 2H, SCH_2), 4.30(t, $J = 8.0$ Hz, 2H, NCH_2), 6.40–6.60 (m, 1H, ArH), 6.80–7.10 (m 3H, ArH), 7.70 (d, $J = 9.0$ Hz, 2H, ArH), 8.15 (d, $J = 9.0$ Hz, 2H, ArH); IR (KBr, cm^{-1}): 1060, 1170, 1200, 1290, 1480, 1570, 1630, 2850, 3100, 3160; MS (EI): m/z 341 (M^+). Anal. calcd for $C_{17}H_{15}N_2O_3S$: C 59.76; H 4.43; N 12.31%. Found C 59.82; H 4.52; N 12.26%.

***N*-(4,5-dihydro-1,3-thiazol-2-yl)-*N*-(4-methoxyphenyl)-4-nitrobenzamide (28, $R_1 = 4\text{-}OCH_3$, $R_2 = 4\text{-}NO_2$).** Yield 68%: mp 131–133 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 3.30 (t, $J = 8.0$ Hz, 2H, SCH_2), 3.70 (s, 3H, OCH_3), 4.25 (t, $J = 8.0$ Hz, 2H, NCH_2), 6.40–6.80 (m, 4H, ArH), 7.65 (d, $J = 9.0$ Hz, 2H, ArH), 8.15 (d, $J = 9.0$ Hz, 2H, ArH), IR (KBr, cm^{-1}): 1050, 1180, 1290, 1490, 1635, 1860, 3140; MS (EI): m/z 357 (M^+). Anal. calcd for $C_{17}H_{15}N_3O_4S$: C 57.13; H 4.23; N 11.76%; Found C 57.20; H 4.25; N 11.78%.

X-ray crystallography

Crystals of general formula $C_{13}H_{11}NO$ (**3′a**) were obtained by slow evaporation of methanol. The structure was revealed as the *N*-phenylbenzamide.

M = 197.23, symmetry monoclinic, space group $P2_1/c$, a = 24.453(8), b = 5.332(1), c = 8.014(1) Å, β = 107.34(2)°β, V = 997.4(2) $Å^3$, Z = 4, $D_c = 1.32$ g cm^{-3}.

Crystals of general formula $C_{14}H_{13}NO_2$ (**3′b**) were obtained by slow evaporation of methanol. The structure was revealed as *N*-(4-methoxy)phenylbenzamide.

M = 227.26, symmetry monoclinic, space group $P2_1/c$, a = 26.766(7), b = 5.244(1), c = 8.126(1) Å, β = 97.56(1)°, V = 1130.6(2) $Å^3$, Z = 4, $D_c = 1.33$ g cm^{-3}.

Crystals of 2-[*N*-(2-methylphenyl)-*N*-benzoyl]amino-4,5-dihydrothiazole($C_{17}H_{16}N_2OS$) (**9**) were obtained by slow evaporation of methanol.

M = 296.40, symmetry triclinic, space group P-1, a = 8.853(1), b = 9.473(1), c = 9.977(1) Å, α = 83.62(1), β = 83.78(1), γ = 62.97(1)°, V = 739.1(1) $Å^3$, Z = 2, $D_c = 1.33$ g cm^{-3}.

A single crystal having approximate dimensions of 0.30×0.20×0.20 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed with Cu*K*α radiation (λ = 1.54184 Å) on an Enraf-Nonius CAD4 computer controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $6 < \theta < 27°$, measured by the computer-controlled diagonal slit method of centering.

Table 6. Final positions ($\times 10^4$) with estimated standard deviations in parentheses, derived from full-matrix least-squares refinement for compound **9**

Atoms	x	y	z
S(1)	675(1)	1028(1)	8485(1)
C(2)	2305(3)	1636(3)	8299(3)
N(3)	3816(3)	604(3)	8456(3)
C(4)	3903(4)	−983(3)	8831(4)
C(5)	2316(4)	−1015(3)	8409(4)
N(6)	1942(2)	3232(2)	7900(2)
C(7)	304(3)	4449(3)	8101(3)
O(8)	−785(2)	4201(2)	8791(2)
C(9)	−103(3)	6044(3)	7403(3)
C(10)	−1268(3)	7363(3)	8078(3)
C(11)	−1807(4)	8875(3)	7432(4)
C(12)	−1217(4)	9064(3)	6119(8)
C(13)	−83(3)	7753(3)	5432(3)
C(14)	481(3)	6244(3)	6075(3)
C(15)	3385(3)	3572(3)	7571(3)
C(16)	4408(3)	3059(3)	6387(3)
C(17)	5777(3)	3424(3)	6135(3)
C(18)	6129(3)	4237(3)	7021(3)
C(19)	5088(3)	4736(3)	8192(3)
C(20)	3713(3)	4402(3)	8468(3)
C(21)	4084(4)	2160(3)	5395(3)

A total of 2514 unique reflections out to $\theta = 65°$ were collected. As a check on crystal and electronic stability, two representative reflections (−124 and 0; 0–5) were measured every 60 min. The intensities of these standards remained constant within experimental error throughout data collection. No decay correction was applied. Lorentz and polarization corrections were applied to the data.

The structure was solved by direct methods using MolEN[21] using 308 reflections (minimum E of 1.560) and 2890 relationships, a total of 16 phase sets were produced. All non-hydrogen atoms were located from the best E-map. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full-matrix least squares. Only the 2184 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 254 variable parameters and converged with unweighted and weighted agreement factors 0.040 and 0.042. The final difference Fourier map showed no significant residual electron density. Final positions of the non-hydrogen atoms and standard deviations are presented in Table 6.

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