Eur. J. Med. Chem. 35 (2000) 351–358

S0223523400001288/SCO

Short communication

Design, synthesis and antihistaminic (H_1) activity of some condensed 3-aminopyrimidin-4(3*H*)-ones

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Received 21 October 1998; revised 28 July 1999; accepted 5 August 1999

Abstract – A novel series of condensed 3-amino-2-(substituted)methylpyrimidin-4(3*H*)-ones is reported with potential H_1 receptor antagonistic activity. The IC_{50} values for 23 compounds were found to be in the micromolar range. Five lead compounds (**10c**, **e**, **g**, **r** and **t**), when evaluated by the in vivo method were found to protect guinea-pigs from the histamine induced asphyxia and antagonized histamine in a competitive and reversible manner. With a pA_2 value of 8.7 and protection time of 9.5 min (in vivo test), compound **10g** was the most active amongst these five compounds. The isosteric replacement of the side chain -NH- in series **1**, by oxygen and -$NHSO_2$- functions, was undertaken to investigate the role of two amino functions in the receptor binding. This isosteric replacement with -O- does not affect the antihistaminic activity and the sedative potential of the series. Preliminary molecular modelling studies indicate that the compounds with -$NHSO_2$- in the side chain exhibit a closer fit with temelastine than their -O- isosteres. © 2000 Éditions scientifiques et médicales Elsevier SAS

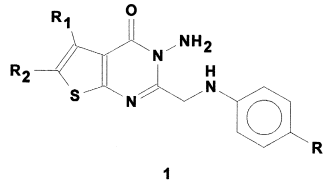
antihistaminics / H_1 antagonists / condensed pyrimidines / molecular modelling

1. Introduction

Antihistaminics (H_1) form a major therapeutic class of drugs used in the treatment of a variety of allergic conditions like rhinitis, urticaria, hay fever and even asthma [1]. The classical antihistaminics are associated with several central side effects, especially sedation [2, 3]. Unlike the classical H_1 antagonists, the newer generation molecules, like terfenadine [4], astemizole [5], cetirizine [6], loratadine [7], ebastine [8], epinastine [9] and temelastine [10] have very poor access to the CNS and therefore are relatively less sedative.

The aromatic rings and a side chain with a basic nitrogen atom are the essential pharmacophoric requirements of H_1 receptor antagonists [11–13]. It explains the antihistaminic activity of several chemical classes of drugs, such as ethylenediamines, aminoethyl ethers, propyl- and propenylamines, phenothiazines, piperidines, and piperazines, on the basis of their chemical and geometrical similarities. This model was recently refined by Ter Laak et al. with the five point pharmacophore model, which better explains the recognition of antagonists belonging to different chemical classes [14] at the receptor. Whereas the previous model takes into account only one stable conformation of the active molecules (based upon X-ray crystallography or global minima), the five point attachment model claims higher rationale as it considers, for the first time, the H-bonding interaction of the receptor aspartate with the protonated nitrogen of the antagonist. Thus the active aspartate-116 residue present in the transmembrane domains II or III of the H_1 receptor is also included in the model [15–18]. Interaction of the Asp-116 with the classical antihistamine mepyramine has been studied [19].

Earlier, the synthesis and QSAR of some potent 2-(substituted)aminomethyl-3-amino-5,6-disubstituted-



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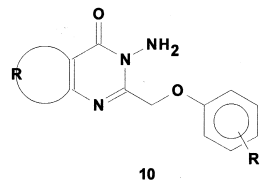

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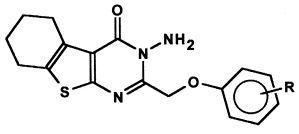
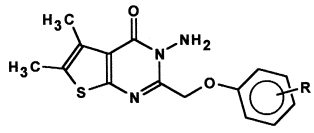
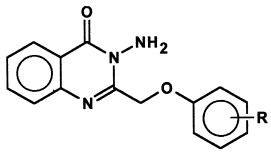
thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**1**) have been reported from this laboratory. It appeared that there are only minimal sedative side effects in this thienopyrimidine series [20]. The target compounds (**1**) were designed according to the classical three point attachment receptor model with the free amino functionality introduced at the N3 of the pyrimidine ring in order to impart the additional polarity. All the compounds were found to antagonize histamine at the H_1 receptor with IC_{50} values in the range of 10^{-7}–10^{-6} M. The dissociation constant (pK_a) of the primary amino group was found to be 7.5 [20].

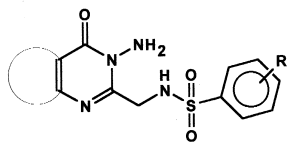
With a view to complete the SAR study of the earlier series (**1**), two different types of modifications were made in the present series. Thienopyrimidines (**10a–o**) and quinazolines (**10p–w**) were synthesized to study the effect of substituents annealed to the pyrimidine. Further, two modifications were brought about in the side chain; -NH- in the side chain was replaced with an ether (**10a–f**, **10i–n** and **10p–u**) and sulphonamido linkage (**10g**, **h**, **o**, **v** and **w**).

Since a protonated site is also required in order to form an ionic (hydrogen) bond with the aspartate-116 residue of the histamine receptor [14], the role of the free amino function at N3 as H-bond donor will also be discussed.









2. Chemistry

The synthesis of the target compounds, 2-(aryloxy) methyl-3-amino-5-6-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and 2-(aryloxy)methyl-3-amino-quinazolin-4(3*H*)-ones (**10a–w**) was achieved by the route depicted in *figure 1*. 4,5-Disubstituted-2-aminothiophene-3-carboxylic esters (**6**) were available through the Gewald reaction [21].

The aryloxy chlorides (**5**) were synthesized from a series of different aryloxyacetic acids (**4**) by refluxing

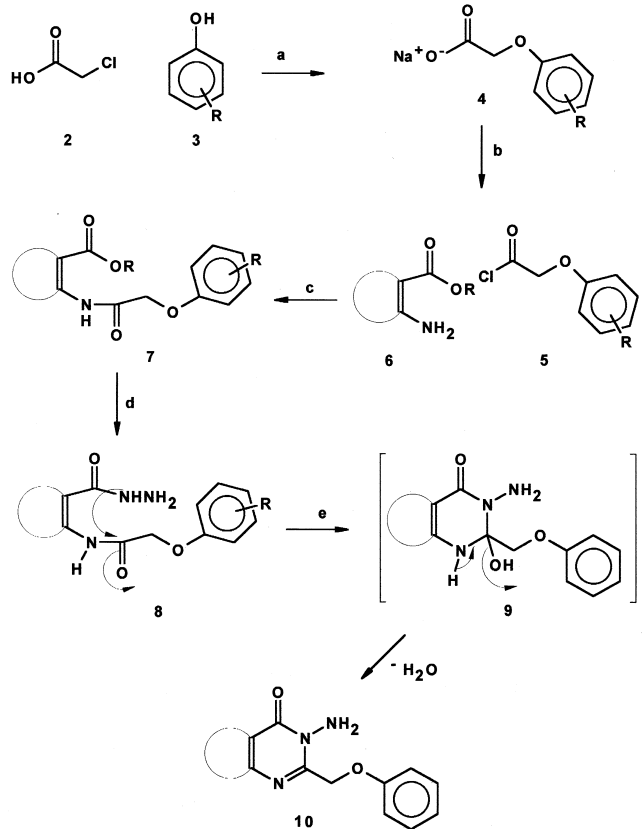


Figure 1. Synthesis of target compounds **10a–w**.
a: aqueous NaOH, reflux; b: $SOCl_2$/benzene, reflux, 4–6 h; c: acetic acid, 0–5 °C, stirring for 4–5 h; d: $N_2H_4.H_2O$, EtOH, reflux, 6 h; e: reflux, 12–14 h.

with thionyl chloride in benzene for 4–6 h. After distilling off the benzene and excess of thionyl chloride under reduced pressure, the desired acid chlorides were obtained as brown viscous liquids which were used directly for the next step.

Various α-aryloxy acetic acids were afforded by displacement of the chloride from the chloroacetic acid (**2**) with different phenols (**3**) under alkaline conditions. The corresponding salts (**4**), thus obtained, were then neutralized to obtain the acids as dark brown viscous liquids and were used as such for the next step.

The esters of 4,5-disubstituted-2-amino-thiophene-3-carboxylic acid or methyl anthranilate (**6**) were subjected to acylation with the various aryloxyacetyl chlorides (**5**) to obtain a series of ethyl 2-(aryloxy)acetamido-5,6-disubstitutedthiophene-3-carboxylates and methyl 2-(aryloxy)acetamido-benzoates (**7**). This acylation pro-

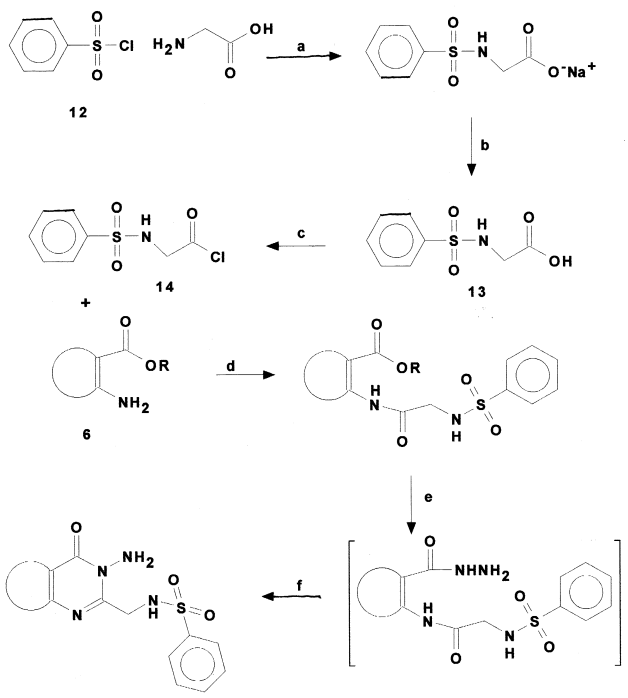


Figure 2. Synthesis of sulphonamido derivatives (**10g**, **h**, **o**, **v** and **w**).
a: KOH/EtOH, reflux; b: HCl, neutralization; c: $SOCl_2$/benzene, reflux, 4–6 h; d: dioxane, TEA, reflux, 4–5 h; e: $N_2H_4.H_2O$, EtOH, reflux, 5–6 h; f: reflux, 12–14 h.

ceeds smoothly in acetic acid in ice cold conditions giving good yields.

The esters (**7**) were then cyclized with hydrazine hydrate to the corresponding target pyrimidines, **10**. The reaction proceeds through the hydrazino intermediates (**8**), which then undergoes the nucleophilic addition with carbonyl carbon of the side chain to the unisoluble intermediate (**9**), followed by the loss of water to afford the target compounds (**10**) (*figure 1*). The typical mass fragmentation data of these compounds shows the presence of a prominent M-16$^+$ (M–NH_2) peak and ^{1}H-NMR shows a sharp singlet for the NH_2 group, exchangeable with D_2O.

The sulphonamido derivatives (**10g**, **10h**, **10o**, **10u** and **10v**) were synthesized by the route shown in *figure 2*. α-(Phenylsulphonamino)acetic acid (**13**) was synthesized by the displacement of chloride from benzenesulphonyl chloride (**12**), by glycine under alkaline conditions and then neutralizing it. Further synthesis of the target compounds is similar to the previous method via the formation of corresponding acid chlorides (**14**).

3. Results and discussion

Compounds synthesized were characterized by spectral and physical data. I.R. spectra show the distinct peaks for amino groups in the range of 3 360–3 300 cm^{-1} (-NH_2), and a sharp peak around 1 660 cm^{-1} (-C=O). The sulphonamido group is charactarized by a sharp absorption in the range of 3 290–3 200 cm^{-1} and two sharp peaks in the range of 1 180–1 150 cm^{-1} and 1 380–1 340 cm^{-1} each. The mass spectra show the molecular ion peak and prominent M-16 peak indicating the early loss of the free amino function at N3. However, in the quinazolines, the prominent peak was obtained by the loss of the side chain aryloxy moiety. Further fragmentation of the molecule was found to be satisfactory.

The ^{1}H-NMR spectra showed the primary amino protons at δ 5.3–5.2 and were D_2O exchangeable. The methylene protons in the side chain were found to resonate at δ 5.3. The aromatic protons in the side chain appear at δ 7.5–7.2. The aliphatic protons of the tetrahydrobenzo and dimethyl substitutions on the thiophene were found at the downfield values as multiplet and two singlets, respectively.

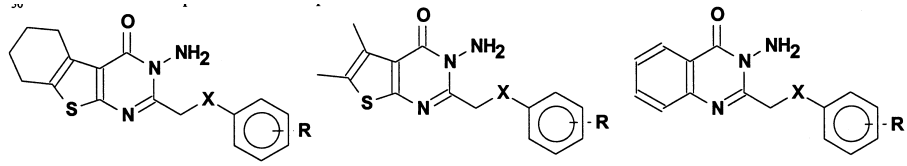
4. Biological activity

When evaluated for the antihistaminic (H_1) activity on the guinea-pig ileum preparation, the compounds **10a–w** were found to exhibit the IC_{50} values in the micromolar range (10^{-6}–10^{-7} M). The sedative potential was less than the standard diphenhydramine and mepyramine, but was higher than cetirizine (*table I*). The typical rightward parallel shifting of the dose–response curve in the presence of antagonists indicates that the inhibition is competitive and surmountable, for the five lead compounds studied (**10c**, **e**, **g**, **r** and **t**). The compounds with a sulphonamido function in the side chain however, exhibited 2–4-fold higher affinity to the receptor than their ether counterparts as is evident from in vivo as well as in vitro tests (*tables I* and *II*).

The five lead compounds (**10c**, **10e**, **10g**, **10r** and **10t**) were evaluated for pA_2 values on the guinea-pig ileum tissue and the lead compound **10g**, a sulphonamido derivative, exhibited maximum activity (pA_2 = 8.7) (*table II*).

When evaluated by the in-vivo method for protection of guinea-pigs from histamine induced asphyxia, lead compounds (**10c**, **10e**, **10g**, **10r** and **10t**) were found to prolong the time for the induction of asphyxia. A sulphonamido derivative, **10g**, showed maximum protection from histamine induced asphyxia (9.5 min) and the activity is

Table I. IC_{50} values and sedative potential for compounds **10a–w**.



10a-h **10i-o** **10p-w**

Compound no.	R	X	IC_{50} value μM ± SEM[a]	% sedation after 1 h[b]
10a	-H	-O-	1.28 ± 0.12	52
10b	-4-CH_3	-O-	1.16 ± 0.10	56
10c	-3-CH_3	-O-	0.62 ± 0.08	49
10d	-4-Cl	-O-	0.59 ± 0.05	56
10e	-3-CH_3,4-Cl	-O-	0.42 ± 0.09	66
10f	-3,4-CH=CH–CH=CH-	-O-	1.80 ± 0.16	75
10g	-H	-$NHSO_2$	0.32 ± 0.02	41
10h	-4-CH_3	-$NHSO_2$	0.36 ± 0.02	39
10i	-H	-O-	0.67 ± 0.05	42
10j	-4-CH_3	-O-	0.79 ± 0.08	46
10k	-4-Cl	-O-	0.44 ± 0.02	36
10l	-3,4-di-Cl	-O-	0.80 ± 0.05	57
10m	-3-CH_3,4-Cl	-O-	0.63 ± 0.06	56
10n	-3,4-CH=CH–CH=CH-	-O-	1.05 ± 0.10	72
10o	-H	-$NHSO_2$-	0.46 ± 0.06	37
10p	-H	-O-	0.66 ± 0.07	39
10q	-4-CH_3	-O-	1.19 ± 0.12	48
10r	-3-CH_3	-O-	2.01 ± 0.19	51
10s	-2-CH_3	-O-	1.04 ± 0.09	49
10t	-4-Cl	-O-	0.44 ± 0.04	47
10u	-3-CH_3,4-Cl	-O-	0.64 ± 0.07	61
10v	-H	-$NHSO_2$-	0.37 ± 0.07	44
10w	-3,4-CH=CH–CH=CH-	-$NHSO_2$-	0.46 ± 0.07	38
Diphenhydramine			0.57 ± 0.09	76
Mepyramine			0.040 ± 0.009	64
Cetirizine			0.037 ± 0.007	21

[a]n = 4–6; [b]n = 5 animals, the difference was found to be significant by students t-test, $P < 0.001$ and S.D. < 7%.

comparable with the standard cetirizine when administered intraperitonially (*table II*).

The higher activity of sulphonamido derivatives can be explained from the molecular modelling results, which show a better fit of these compounds with temelastine than the ether derivatives. The better fit, as is reflected in the lesser r.m.s.d. is essentially because of the increased side chain length of sulphonamides (figures *3* and *4*).

The same five representative compounds (**10c**, **10e**, **10g**, **10r** and **10t**) were also evaluated for acetylcholine antagonism (*table II*). For all the five compounds, pA_2-histamine (7.2–8.7) was found to be much higher than pA_2-acetylcholine (5.1–6.1) which indicates more than 200-fold greater affinity of the molecules to histamine receptors than to the acetylcholine receptors when tested on guinea-pig ileum, thus indicating their high degree of selectivity.

However, the compound **10g**, as compared to **1**, was found to have very low in vivo activity when given orally rather than by the intraperitonial route. The lesser oral activity of the compound **10g** may be due to the cleavage of sulphonamide at gastric pH.

5. Molecular modelling

In order to investigate the possible reasons for the higher activity of the sulphonamido derivative, the conformational analysis for the most active derivative was

Table II. pA_2 values and in vivo results in the guinea-pig.

Compound no.	pA_2 (histamine)[a] Guinea-pig ileum	pA_2 (Ach)[a] Guinea-pig ileum	Protection from histamine induced asphyxia (time in minutes)[b]	
			Control	Treated
10c	7.94 ± 0.11	5.6 ± 0.14	2.53	6.84
10e	8.17 ± 0.09	5.1 ± 0.16	2.64	7.68
10g	8.73 ± 0.08	5.9 ± 0.11	2.59	9.56
10r	8.26 ± 0.12	6.1 ± 0.17	2.81	7.34
10t	8.63 ± 0.12	5.7 ± 0.12	2.41	8.95
DPH	7.61 ± 0.13	6.7 ± 0.15	2.34	6.42
Cetirizine	8.86 ± 0.10	6.34 ± 0.14	2.43	9.81

[a]Determined by Schild plot, $n = 4–6$; [b]The differences between the mean time ($n = 4$) were found to be significant by *t*-test, $P < 0.001$, DPH: Diphenhydramne.

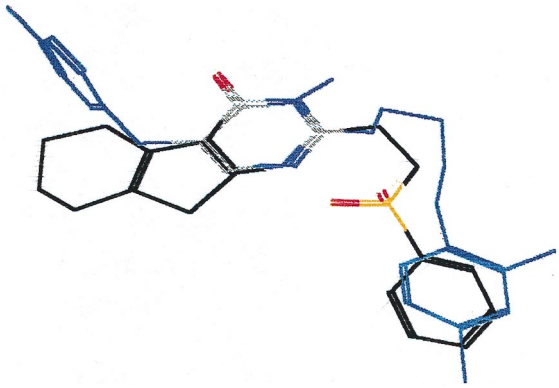


Figure 3. Blue: temelastine; black: **10g**, r.m.s.d. = 0.13.

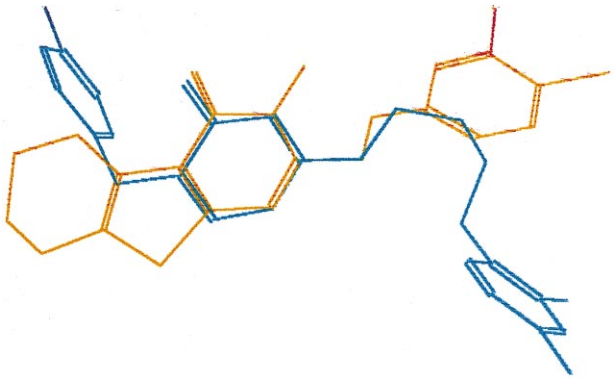
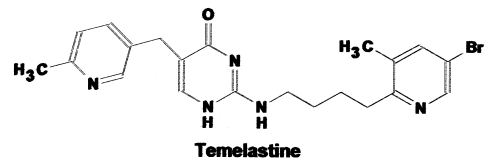


Figure 4. Blue: temelastine; red: **10e**, showing unfavourable orientation of the sidechain aryl ring, r.m.s.d. = 0.24.

carried out. The conformations of **10g** and temelastine were generated using the AM1 method in CS ChemOffice software [22]. Molecular dynamics were performed with the step interval of 2.0 fs and heating rate of 1 kcal/atom/ps. The minimum energy conformations of both the molecules were generated by the MOPAC–AM1 method overlapping at the possible pharmacophoric points, viz, the corresponding positive centres, and the centroids of side chain aromatic rings. Compound **10g** shows reasonable conformational similarity with temelastine (r.m.s.d. = 0.13, *figure 3*) as against **10e** (r.m.s.d. = 0.24, *figure 4*). The overlapping of low energy conformers shows that the side chain pyridine ring of temelastine and the side chain aromatic ring of **10g** falls in the same contour. On the other hand, the aromatic ring of the ether derivative, **10e** is unable to overlap with the pyridine of temelastine at the energy minima, resulting in higher r.m.s.d. The better fit of **10g** with temelastine is essentially due to the increased spacer length in the side chain.



Temelastine

Molecular modelling studies also reveal that the aromatic ring of the sulphonamido derivative **10g**, and side chain pyridyl ring of temelastine stays in *trans*-like conformation at energy minima. For the ether derivative **10e**, the side chain aromatic ring deviates away from these contours and the *trans*-like conformations exist only at slightly higher energy.

6. Experimental

6.1. General

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in potassium bromide on a Perkin Elmer 841 grating spectrophotometer (Perkin-Elmer, USA). The mass spectra were obtained on a Varian Atlas CH-7 spectrometer at 70 eV ionizing beam, using direct insertion probe. Satisfactory microanalysis (± 0.4% of the calculated values) was obtained for all the compounds.

The 2-aminothiophene-3-carboxylic acid ethyl esters were synthesized according to the literature method [21]. All the other reagents were of reagent grade.

*6.1.1. Synthesis of the aryloxyacetic acids (**4a–f**)*

Accurately measured quantities of chloroacetic acid (0.05 mol) and an appropriate phenol (0.05 mol) were taken in a conical flask. An aqueous solution of sodium hydroxide (0.12 mol in 25 mL water) was slowly added to it with constant stirring. Considerable amounts of heat evolve during the reaction. Stirring was continued for 2 h and after the solution turned clear, greenish or yellow, the whole reaction mixture was evaporated in an evaporating dish until the solid sodium salt precipitated out. The salt was isolated and dried. The salt was then dissolved in water and concentrated hydrochloric acid was added dropwise till the congo-red paper turned blue. The precipitated aryloxy acetic acid was filtered off and recrystallized from water.

*6.1.2. Synthesis of aryloxyacetyl chlorides (**5a–f**)*

An accurately weighed quantity of the appropriate aryloxyacetic acid (0.05 mol) was dissolved in benzene in a round bottomed flask, to which thionyl chloride (0.1 mol) was added. The reaction mixture was refluxed for 5–6 h. After completion of the reaction (TLC), excess of thionyl chloride and benzene were distilled off completely under the reduced pressure. The aryloxyacetyl chloride, which remains behind as a dark yellow to brown (depending on the aryloxyacetic acid) viscous liquid, was immediately used for the next step.

*6.1.3. Synthesis of the ethyl 2-(aryloxy)acetamidothiophene-3-carboxylate/benzoates (**8a–f**, **8i–n** and **8p–u**). General procedure*

A solution of ethyl 2-amino-4,5-disubstituted-thiophene-3-carboxylate (0.02 mol) was prepared in glacial acetic acid and was kept stirring in an ice-bath (0–5 °C). To this well stirred solution was added the aryloxyacetyl chloride (0.02 mol) gradually, ensuring thorough stirring of the entire mixture. The reaction mixture was stirred vigorously for 1 h maintaining the cold conditions throughout the course of reaction. The reaction mixture was then poured into ice-cold water with stirring. The solid separated was filtered off and crystallized from a cyclohexane/chloroform mixture.

*6.1.4. Synthesis of the ethyl 2-(phenylsulphonamido)-4,5-disubstituted thiophene-3-carboxylates and benzoates (**8g**, **8h**, **8o**, **8v** and **8w**). General procedure*

A solution of the appropriate ethyl 2-(aryloxy) acetamidothiophene-3-carboxylate/benzoates (0.02 mol) was prepared in glacial acetic acid (20 mL) and was kept stirring in an ice-bath (0–5 °C). To this well stirred solution was added 1-(phenylsulphonylamino)acetyl chloride (0.02 mol) gradually, ensuring thorough stirring of the entire mixture. The reaction mixture was stirred vigorously for 30–45 min maintaining the cold conditions throughout the course of reaction. About 100 mL of ice-cold water was added to the reaction while continuing the stirring. The light brown coloured solid obtained was filtered off, washed with water and recrystallized from cyclohexane.

*6.1.5. Synthesis of 2-phenoxymethyl-3-amino-5,6,7,8-tetrahydrobenzo(b)thieno[2,3-d]pyrimidin-4(3H)-one (**10a**)*

To an accurately weighed quantity of ethyl 2-phenoxyacetamido-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate (**8a**) (0.01 mol, 3.8 g) in a round bottomed flask was added approximately 20 mL of hydrazine hydrate (99%). The reaction mixture was then refluxed for 16–20 h. After completion of the reaction (TLC), the reaction mixture was allowed to stand at room temperature. The compound was allowed to crystallize, then filtered off, washed with ethanol/water (1:1) and recrystallized from ethanol/chloroform. Yield: 1.9 g, 58%, m.p. 168–170 °C, IR (KBr, cm^{-1}) 3 354, 3 301, 1 650; MS (m/z): 327 (M^+), 311, 250, 234, 93, 77; ^{1}H-NMR (δ ppm) δ 5.2 (s) 2H, NH_2 (D_2O exchange), δ 2.4–1.8, (m), 8H, $CH_2CH_2CH_2CH_2$- on thiophene, δ 5.3, (s) 2H, -CH_2O-, δ 7.5–7.2, (m), 5H, Ar–H; Microanalysis: % calc. (found) C 62.39 (62.51), H 5.20 (5.43), N 12.84 (12.76).

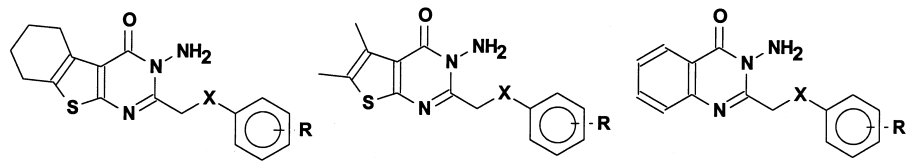
All the target compounds (**10a–w,** *table III*) were synthesized by the above procedure and characterized.

6.2. Biological activity

6.2.1. H_1-antagonistic activity [23, 24] (IC_{50} and pA_2)

H_1-antagonistic activity of this series (**10**) was determined in terms of IC_{50} values and pA_2 values on the guinea-pig ileum tissue. The animals were fasted for 24 h prior to use. Responses were taken on the 2 cm long

Table III. Physical characteristics of compounds **10a–w**.



10a-h **10i-o** **10p-w**

Compound no.	R	X	Mol. formula	Mol. wt.	M.p.	% Yield*
10a	-H	-O-	$C_{17}H_{17}N_3O_2S$	327	168–70	20
10b	-4-CH_3	-O-	$C_{18}H_{19}N_3O_2S$	341	122–24	22
10c	-3-CH_3	-O-	$C_{18}H_{19}N_3O_2S$	341	157–59	15
10d	-4-Cl	-O-	$C_{17}H_{16}ClN_3O_2S$	361.5	165–66	21
10e	-3-CH_3,4-Cl	-O-	$C_{18}H_{18}ClN_3O_2S$	375.5	158–60	18
10f	-3,4-CH=CH–CH=CH-	-O-	$C_{21}H_{19}N_3O_2S$	377	194–95	18
10g	-H	-$NHSO_2$	$C_{17}H_{18}N_4O_3S_2$	390	192–94	10
10h	-4-CH_3	-$NHSO_2$	$C_{18}H_{20}N_4O_3S_2$	404	186–87	14
10i	-H	-O-	$C_{15}H_{15}N_3O_2S$	301	159–61	23
10j	-4-CH_3	-O-	$C_{16}H_{17}N_3O_2S$	315	176–77	19
10k	-4-Cl	-O-	$C_{15}H_{14}ClN_3O_2S$	335.5	173–75	20
10l	-3,4-di-Cl	-O-	$C_{15}H_{13}Cl_2N_3O_2S$	370	196–97	24
10m	-3-CH_3,4-Cl	-O-	$C_{16}H_{16}ClN_3O_2S$	349.5	183–84	23
10n	-3,4-CH=CH–CH=CH-	-O-	$C_{19}H_{17}N_3O_2S$	351	233–35	18
10o	-H	-$NHSO_2$-	$C_{15}H_{16}N_4O_3S_2$	364	196–98	17
10p	-H	-O-	$C_{15}H_{13}N_3O_2$	267	160–62	26
10q	-4-CH_3	-O-	$C_{16}H_{15}N_3O_2$	281	95–97	32
10r	-3-CH_3	-O-	$C_{16}H_{15}N_3O_2$	281	140–42	29
10s	-2-CH_3	-O-	$C_{16}H_{15}N_3O_2$	281	162–63	38
10t	-4-Cl	-O-	$C_{15}H_{12}ClN_3O_2$	301.5	126–28	46
10u	-3-CH_3,4-Cl	-O-	$C_{16}H_{14}ClN_3O_2$	315.5	164–66	48
10v	-H	-$NHSO_2$-	$C_{15}H_{14}N_4O_3S$	330	172–74	39
10w	-3,4-CH=CH–CH=CH-	-$NHSO_2$-	$C_{19}H_{16}N_4O_3S$	382	180–82	34

* Overall yields.
Elemental analysis (C, H, N) for all the compounds was found to be satisfactory (± 0.4%).

pieces of ileum in physiological salt solution at 36 °C. The method involves the blocking of responses of histamine (5×10^{-5} M, submaximal dose) induced contraction by the antagonists at different logarithmically increasing dose levels. Equilibration time of 4 min was allowed after each dose of antagonist and each response was repeated 4–6 times. A graph was plotted between the log dose of antagonist vs. percentage inhibition and the IC_{50} values were calculated by interpolation.

pA_2 values for the five representative compounds (**10c**, **10e**, **10g**, **10r** and **10t**) were calculated by the Schild plot method. The dose–response curves of histamine were taken in the absence and presence of antagonist at 4–6 different concentrations and the dose ratios were calculated. The plot of log dose ratio vs. –log of molar concentration gave the pA_2 values by interpolation (*figure 5*).

6.2.2. Sedative potential [23]

The sedative potential of the compounds was tested on albino mice using the photoactometer method. Animals were divided into groups of five. The samples were prepared by suspending the compounds in 1% aqueous sodium CMC (carboxymethylcellulose) and were administered intraperitonially. Each group of five animals was treated with the compounds (dose, 8 mg/kg body weight) and the photoactometer readings were taken after 0.5 and 1.0 h of treatment. The same group of animals was used

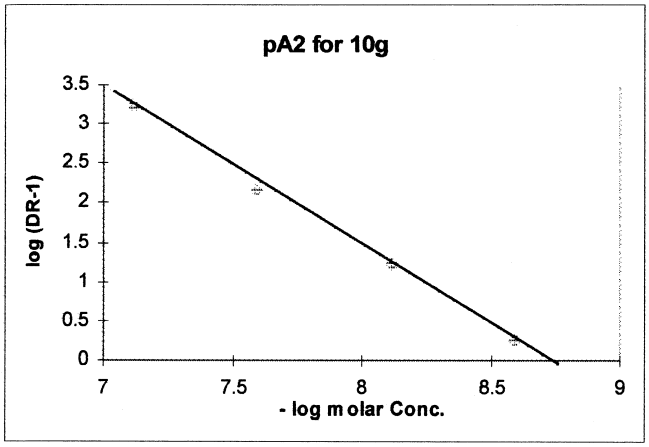


Figure 5. Compound **10g**, pA_2 = 8.73.

as control. The percentage fall in the photoactometer count was taken as the measure of sedative activity. Students *t*-test was applied and the difference in the treated and control readings was found to be highly significant, $P < 0.001$. The percentage fall in photoactometer reading is reported as the extent of sedation produced (*table I*). Percent standard deviation was found to be less than seven for all the compounds.

Acknowledgements

One of the authors (V.S.S.) is thankful to the Council of Scientific and Industrial Research, New Delhi, for the financial support of this project.

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