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Research Article

SYNTHESIS OF SOME NOVEL SUBSTITUTED 2-AMINOTHIOPHENES AND EVALUATION FOR THEIR ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

2-aminothiophene forms a significant class of drugs which exhibits the excellent biological activities like anti-inflammatory, antifungal, analgesic, antibacterial, anticancer and antiviral activities. In continuation of our previous vast research on 2-Aminothiophene,the present study is aimed on synthesis of 2-amino 4,5,6,7 tetra hydro benzo[*b*] thiophene-3-carboxylic ethyl ester derivatives and are characterized by using spectral studies. These derivatives were also screened for their anti-inflammatory activity using carageenan induced rat paw edema using indomethacin as standard. In present research work, the derivatives which are having pyridine substitution [2_e] and hydroxyl group [2_c] shown significant anti-inflammatory activity. The derivatives [2_a, 2_b, 2_d] containing thiophene were shown moderate activities.

Keywords: 2-amino thiophenes, Gewald Synthesis, Anti-inflammatory activity, Carrageenan.

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INTRODUCTION

The rapid development of resistance to existing anti-inflammatory drugs leads a major threat to public health. Consequently there is a necessity to develop new anti-inflammatory agents with potent activity [1]. Among the broad range of templates heterocyclic compounds represent the most promising molecules as leading structure for the discovery of novel synthetic drugs [2]. In particular the classes of compounds bearing 2-aminothiophenes and its derivatives have been the focus of greatest interest because of their remarkable biological properties including anti-inflammatory, antifungal, analgesic, antibacterial and antiviral activities. 2-aminothiophenes have become a well privileged class

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of compounds in drug discovery programmes and the interest in developing this class of bioactive compounds remain high in a medicinal chemistry [3]. Considering all these biological activities of 2-aminothiophenes which were reported to be more potent and less toxic [4].To take up the present investigation in an effort to synthesize novel 2-aminothiophene derivatives as anti-inflammatory agents [5]. We utilized 2-aminothiophene as key prototype and the newly synthesized compounds were evaluated for their anti-inflammatory activity by carrageenan induced rat paw edema using indomethacin as standard [6].

MATERIALS AND METHODS

Chemistry

Solvents and reagents were obtained from commercial sources and were dried and purified when necessary by standard procedure. The melting points were determined with an electro thermal melting point apparatus. Infrared spectra (KBr disc) were carried out on FTIR-8400 Shimadzu and the frequencies were expressed in cm-1. 1H NMR spectra were recorded on Bruker-Avance 400 MHz instrument with TMS (0 ppm) as an internal standard; the chemical shifts (δ) are reported in ppm and coupling constants (J) are given in Hertz (Hz). Signal multiplicities are represented by s(singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet) and br s broad singlet). All the solvents and reagents were used without further purification.

General procedure for the synthesis of starting material 2-aminothiophene (1)

To a mixture of ketone (0. 15 mol) and ethylcyanoacetate (0. 15 mol) were dissolved in 200 mL of absolute ethanol. Sulphur powder (0. 15 mol) and diethyl amine (20 mL) were added. The mixture was heated at 50 °C during 3 hours and then was cooled in refrigerator for 24hrs.During the cooling the formed solid was separated out. The precipitate was collected and recrystalized with cold ethanol [9-12].

General procedure for the synthesis of substituted 2-aminothiophene derivatives (2a-e)

Dissolve 0.03M of 2-aminothiophene (1) and 0.03M of aldehydes (a-e),25ml of dry Dimethylformamide and HCl 0.2ml was taken in a round bottomed flask for condensation and allow the reaction mixture to reflux for 5hrs. Then the reaction mixture was stand overnight in the refrigerator then the reaction mixture was poured into crushed ice and stirred, the solid thus obtained was filtered off and washed withcold water andrecrystallized with ethanol [7,8].

Ethyl 2-(4-chlorophenylamino)-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (2_a) Yield 76%, M.P 203^0 C,3277.12 (N-H str), 1632.43(C-C str) ; 1683.81 (C=O) ; 1263.42 (C-N)**,1H NMR (CDCl3) δ: -**1.30 {S, H of CH_3}, 1.61{d, H of CH_2}, 1.62{d, H of CH_2}5.96 {t, H of CH (H3)}, 4.0 {m,2H of$C- NH_2$}, 4.29 {m, 3 H of CH_2}, 2.28 {s, 3H of CH_3}, Anal. calcd: C,60.80;H,5.40;Cl,10.56;N,4.17;O,9.53;S,9.55.

Ethyl 2-(4-nitrophenylamino)-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (2_b) Yield 79%, M.P 217^0 C, 3232.17 (N-H str), 1673.43(C-C str) ; 1718.81 (C=O); 1310.42 (C-N), **1H NMR (CDCl3) δ: -**1.32 {S, H of CH_3}, 1.61{d, H of CH_2}, 1.62{d, H of CH_2},2.55 {t, H of CH_2 (H3)}, 2.55 {t, H of CH_2 (H3)} 4.01 {m,C- NH}, 4.26 {m, C=O}, 13.44{m, of CH},15.88{m, of CH}.Anal. calcd C, 64.33; H, 6.03; N, 4.41; O, 15.12; S, 10.10.

Ethyl 2-(4-hydroxyphenylamino)-4, 5, 6, 7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (2_c),Yield 78%, M.P 236^0 C, 3185.19 (N-H str), 1642.03(C-C str) ; 1721.51 (C=O) ; 1193.24 (C-N), **1H NMR (CDCl3) δ: -**1.31 {S, H of CH_3}, 1.61{d, H of CH_2}, 1.62{d, H of CH_2},2.55 {t, H of CH_2 (H3)}, 2.55 {t, H of CH_2 (H3)} 4.01 {m,C- NH}, 4.29{m, C=O},12.58{m, of CH},12.96{m, of CH},Anal calcd C, 64.33; H, 6.03; N, 4.41; O, 15.12; S, 10.10.

Ethyl 4, 5, 6, 7-tetrahydro 2-(thiophen-2-ylamino)benzo[*b*]thiophene-3-carboxylate (2_d) Yield 76%, M.P 232^0 C, 3255.10 (N-H str), 1611.00(C-C str) ; 1733.66 (C=O) ; 1293.42 (C-N), **1H NMR (CDCl3) δ: -**1.31 {S, H of CH_3}, }, 1.61{d, H of CH_2}, 1.62{d, H of CH_2},2.55 {t, H of CH_2 (H3)}, 2.55 {t, H of CH_2 (H3)} 4.01 {m,C- NH}, 4.29{m, C=O},6.01{m, Hof S},6.51{m, of CH},6.35{m, of CH},Anal calcd C, 58.60; H, 5.57; N, 4.56; O, 10.41; S, 20.86.

2-(piperidine-4-ylamino)-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carboxylicacid ethylester (2_e) Yield 78%, M.P 230^0 C, 31567.19 (N-H str), 1652.23(C-C str) ; 1742.18 (C=O) ; 1353.88(C-N) **1H NMR (CDCl3) δ: -**1.31 {S, H of CH_3}, 1.62{d, H of CH_2},1.62{d, H of CH_2},2.55 {t, H of CH_2 (H3)}, 2.55 {t, H of CH_2 (H3)} 4.01 {m,C- NH}, 4.29{m, C=O},2.63{t, Hof CH},1.69{d, H of CH_2},6.51{m, of CH},2.74{d, H of CH_2},2.01 {m,C-NH},2.75{m, of CH_2},Anal calcd C,62.30; H,7.84; N, 9.08; O, 10.37; S,10.40.

Anti-inflammatory activity by Carageenan Induced Paw Edema in Rats

All the protocols of animal experiments have been sanctioned by the Institutional Animal Ethics Committee (IAEC) Reference No: 1694/PO/a/CPCSEA. Acute anti-inflammatory activity was evaluated by carageenan-induced rat paw edema method. Wistar albino rats were divided into different groups of six rats each. Acute inflammation was produced by injecting 0.1 ml of 1% carageenan into sub- plantar surface of rat hind paw. The control group received tween 80 (0.5%) 0.1ml. The test groups received 50mg/kg of synthesized compounds respectively by oral route. The standard group received the drug Indomethacin 100mg/kg by oral route. All the suspensions were administered 30min before carrageenan injection (0.1ml of 1%). The paw volume, upto the tibiotarsal articulation was measured using a plethysmometer at 30min, 1, 2, 3, & 4 h. The percentage inhibition of paw edema was calculated by using the following formula.

Percentage protection = [(Control-Test)/Control] X 100.

Derivatives of 2-aminothiophenes

Table 1. Physico chemical properties

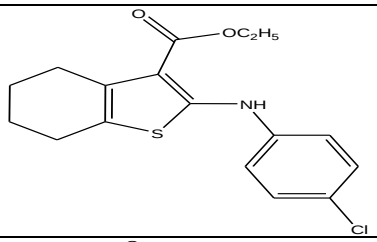
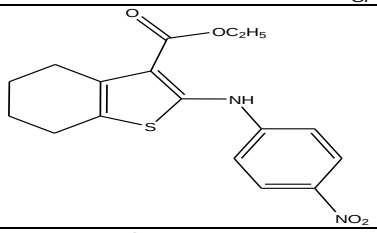
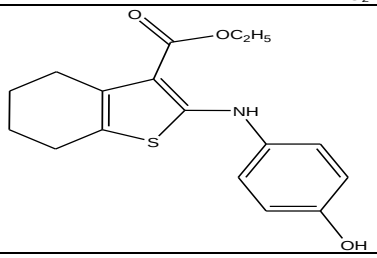
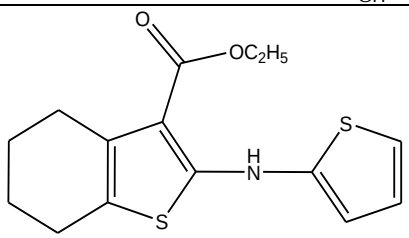
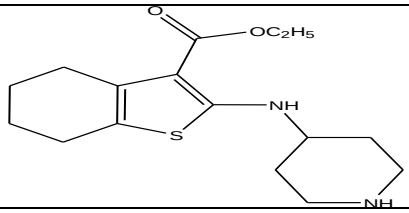
Compound structure	Molecular formula	Molecular weight	Percentage yield	Melting point ^{0}C	$R_f$values
	$C_{17}H_{18}ClNO_2S$	335	76%	203	0.75
	$C_{17}H_{18}N_2O_4S$	346	78%	217	0.69
	$C_{17}H_{19}NO_3S$	317	79%	236	0.65
	$C_{15}H_{17}NO_2S_2$	307	76%	232	0.71
	$C_{16}H_{23}N_2O_2S$	308	78%	230	0.69

Table 2. Anti-inflammatory activity of 2-aminothiophene derivatives by carrageenan induced rat paw edema

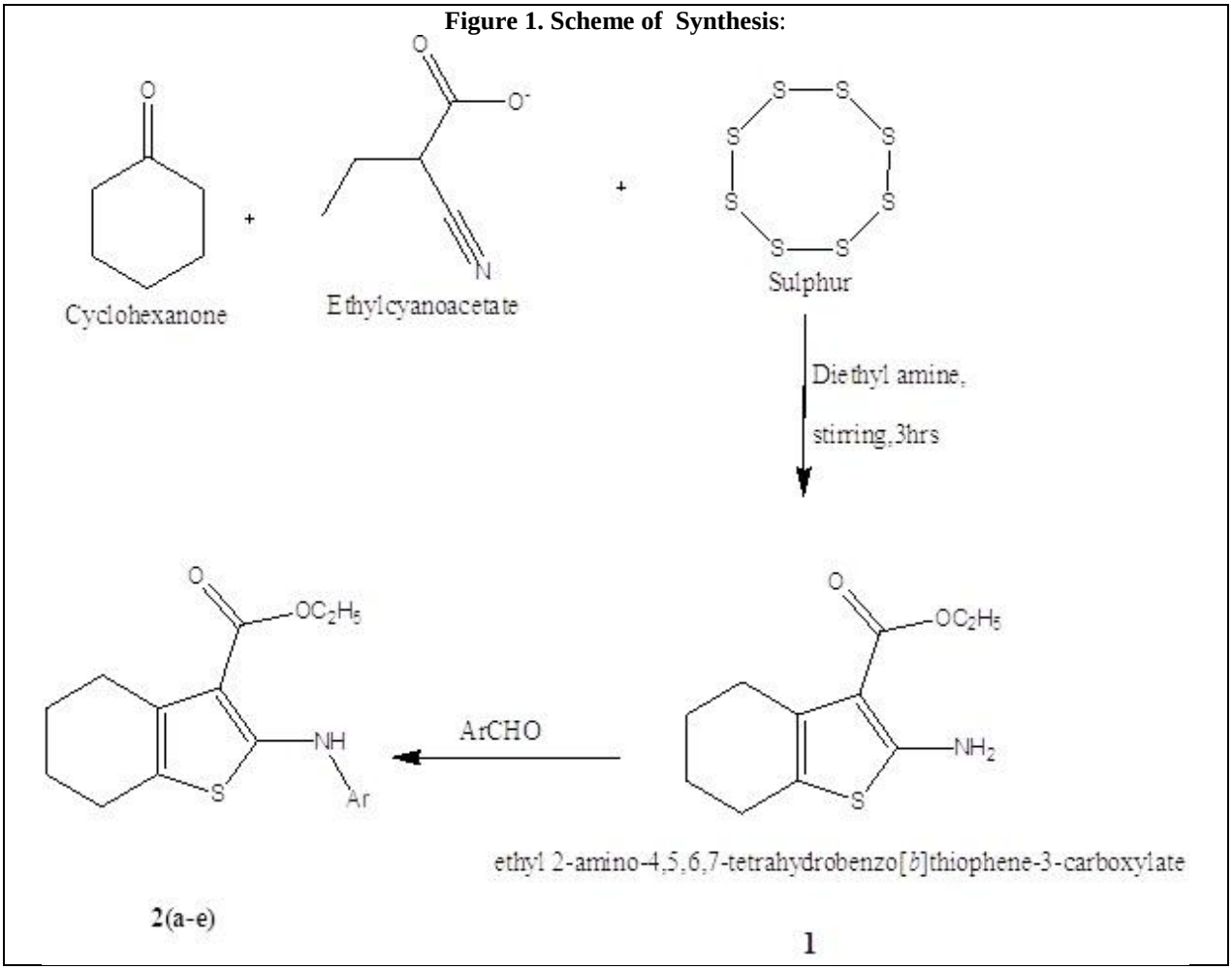
Group	Dose Mg/kg	% Increase in Paw Volumes (ml × 1000) ± SEM (percent inhibition				
		30m	1hr	2hr	3hr	4hr
Control		0.23±0.01	0.36±0.04	079±0.13	0.66±0.04	0.71±0.13
2_a	50	0.16±0.02	0.22±0.02	0.31±0.04	0.25±0.01	0.28±0.02
2b	50	0.15±0.02	0.27±0.03	0.27±0.02	0.23±0.01	0.32±0.02
2c	50	0.17±0.02	0.23±0.02	0.32±0.04	0.28±0.01	0.32±0.03
2d	50	0.18±0.03	0.25±0.03	0.29±0.02	0.27±0.02	0.29±0.03
2e	50	0.15±0.03	0.18±0.05	0.30±0.06	0.22±0.03	0.27±0.04
Standard	100	0.19±0.02	0.21±0.003	0.29±0.06	0.31±0.03	0.35±0.03

*Edema volume (mean±SEM) Probability values (calculated as compared to control using one way-ANOVA followed by Dunnet's Test): **P<0.001All values are means of individual data obtained from six rats (n = 6)

Table 3. Percentage protection against edema formation

Name of the drug	Dose	30min	1hr	2hr	3hr	4hr
Standard(indomethacin)	100	26	41	53	63	50
2_a	100	27	33	51	63	51
2b	100	23	28	43	55	43
2c	100	28	36	54.5	65.4	53.3
2d	100	25	31	47	58	49
2e	100	34.7	49	62	66.6	59.6

Figure 1. Scheme of Synthesis:



Statistical analysis

Data were analyzed by one-way ANOVA followed Dunnett's test and *P* values <0.001 were considered statistically significant.

RESULTS & DISCUSSION

Statistical Analysis: Values are expressed as mean ± standard deviation and statistical analysis was carried out by one way ANOVA. P<0.01 is considered as significant. A new series of 2-aminothiophene derivatives have been synthesized and screened for anti-inflammatory activity by carageenan induced paw edema in rats. The result of anti-inflammatory activity is presented in the Table-2. Table 2 shows the percentage protection in paw volume of rats at 30min, 1hr, 2hr, 3hr, 4hr.From the table it can be observed that the standard (Indomethacin)has protected to an extent of 26,41,53,63,50against inflammation induced by carrageenan at 30min, 1hr, 2hr,3hr,4hrs. All two tests could exhibit more activity at dose i.e. 100mg/kg body weight. Test of 2_a,2_b,2_c,2_d,2_e 100 mg/kg body weight maximum effect exhibited 2b at 3hr (66.6) by comparable to that indomethacin (100mg/kg body weight) showed a significant (p<0.001). The carrageen induced rat paw edema is a biphasic process. The release of histamine or serotonin occurs in the first phase and the second phase is associated with the production of bradykinin, protease, prostaglandin, and lysosome. Therefore, the inhibition of carrageen an-induced inflammation by the test drugs of of 2_a,2_b,2_c,2_d,2_e could be due to the inhibition of the enzyme cyclooxygenase and subsequent inhibition of prostaglandin synthesis. The present study on test drugs 2_a,2_b,2_c,2_d,2_e has demonstrated that significant anti-inflammatory properties and it justifies the use in the treatment of various types of pain and inflammation.

CONCLUSION

In continuation of our research program on 2-aminothiophene, the present study focused on synthesizing 2-aminothiophene derivatives possessing different heterocyclic rings.

The present study has given deep insight as the 2-aminothiophene bearing 4-pyridine ring shown significant anti-inflammatory activity. In the light of results of this study the further research will be carried out considering each heterocyclic ring individually with the 2-aminothiophene ring.

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