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Novel thiophene derivatives as Anti-inflammatory agents

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ABSTRACT:

Thiophene derivatives are associated with broad spectrum of biological activities. In view Synthesis ethyl 3-amino-4-cyano-5-(substituted)thiophene-2-carboxylates were synthesized and tested for *in-vivo* Anti-inflammatory activity by carageenan induced rate paw edema method. The synthetic scheme of the prepared compounds is given. All the synthesized compounds were characterized by using IR, MS and 1H NMR spectroscopy. Compounds were screened for their *in-vivo* Anti-inflammatory: compound 1c showed maximum inhibitory activity. Ibuprofen is used as standard.

KEYWORDS: Synthesis;Thiophene;Anti-inflammatoryactivity,H+/K+-ATPase,COXinhibitors

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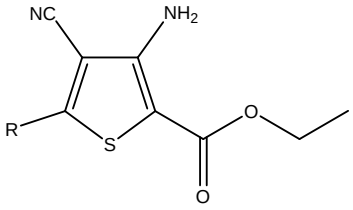
INRODUCTION

Inflammation is a complex multifactorial process as hallmark of many inflammatory diseases. The inflammatory process involves a series of events that can be elicited by numerous stimuli (e.g. Infectious agents, ischemia, antigen antibody interaction and thermal or other physical injury). The response usually accompanied by the familiar clinical signs of erythema, edema, tenderness, pain. Eicosanoid are extremely potent compounds which involved in most type of inflammation and are formed almost in every tissues of the body. Arachidonic acid is the precursor for prostaglandins, thromboxanes and leukotriens. Arachidonic acid is released by the action of phospholipids A_2.[1] PGs derived from the action of COX-1 are considered to be constitutive. They are important for platelet aggregation, renal blood flow in the kidney and cytoprotection on stomach. PGs derived from COX-2 are inducible and upregulated in area of Inflammation. NSAIDs act as anti-inflammatory agents by inhibition of biosynthesis of the PGs that are classified as inflammation inducing substances. For a given drug to act as an NSAID, the drug's chemistry must fulfill two major criteria: Lipophilicity and the presence of an acidic functional group. Drugs having either weak lipophilic or weak acidic properties are not expected to be good anti-inflammatory agents. Acetaminophen shows weak properties regarding both lipophilicty and acidity; therefore, it is void of any anti- inflammatory effects only at much higher doses (10 g) than its analgesic dose of 1gm.2-5 Drugs with both strong lipophilic characteristics and strong acidic properties such as members of the acetic and propionic acid series show significant ant-inflammatory actions at much smaller doses (30 mg -100 mg).2 Most known NSAIDs act as non-selective inhibitors of the enzyme COX - they inhibit both the COX-1 and COX-2 isoenzymes.[6-8]

Variety of biological activity such as analgesic, anti-inflammatory, local anesthetic, antipyretic, tranquilizing, immunosuppressant, antibacterial, antihypertensive and lipid lowering have been exhibited by thiophene derivatives.[9-10]

A series of 2-amino-2carbethoxy-4-cyano-5-(substituted)thiophene (1) was designed on the basis of indirect type of molecular modeling studies.

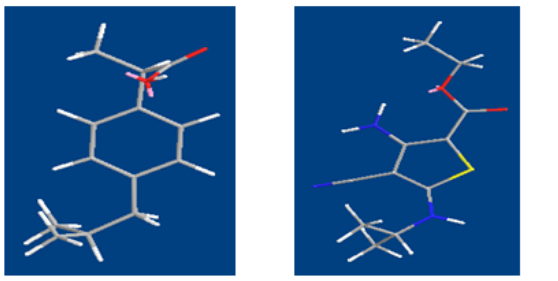


(1)

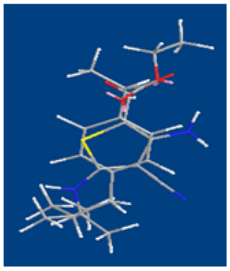
MOLECULAR MODELING

3D structure similarity between 3-amino-2-carbethoxy-4-cyano-5-(isopropyl amino)thiophene **(125)** and Ibuprofen was studied by indirect molecular modeling, structure were generated, energy minimized, superimposed using Chem Office 3D PRO (ver. 5, Cambridge Soft Inc., USA).

3D Structure of Ibuprofen **3D Structure of design series**

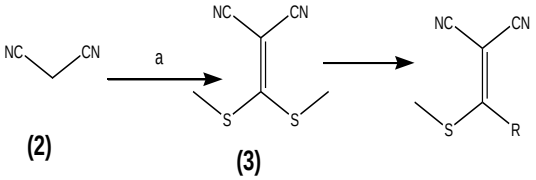


Superimposed structures of ibuprofen and compound (125a)

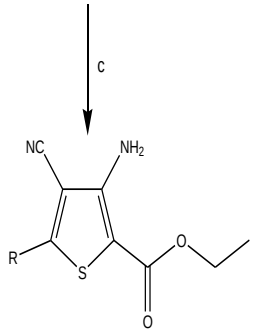


Low rmsd (0.255) suggested good 3D structural similarity between designed series and ibuprofen

Synthetic Scheme



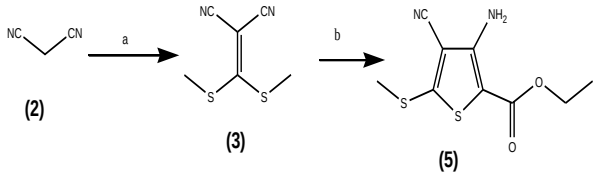
(2) (3) (4)



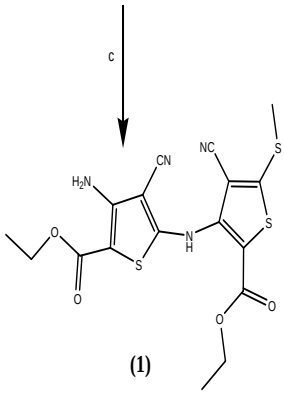
(1)

a = i) KOH, DMF ii) CS_2 iii) DMS, stir at 0 - 5 ° C
b = RH, isoprorpylalcohol
c = $HSCH_2COOC_2H_5$, K_2CO_3, acetone, reflux

R= Dimethylamine, Diethylamine, 3-Trifluomethyl Aniline, 4-Trifluomethyl Aniline, Isopropxyl



(2) (3) (5)



(1)

a =i) KOH, DMF ii) CS_2, iii) DMS, stir, 0 - 5 ° C
b = $HSCH_2COOC_2H_5$, K_2CO_3, acetone, reflux
c = isopropylamine, DMF, reflux

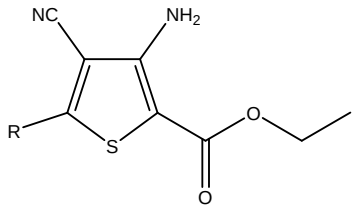
Materials and methods

All the melting points were determined in open capillaries in microprocessor based melting point apparatus model VMP-D (Veego make) and are uncorrected. Infrared spectra were recorded in KBr on 8400S Shimadzu Fourier Transform spectrophotometer. Proton Nuclear Magnetic Resonance spectra were taken

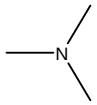
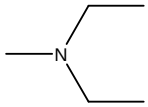
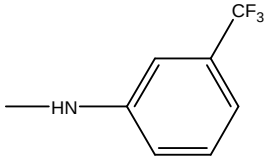
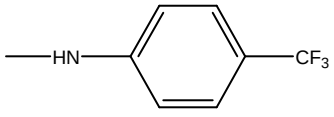
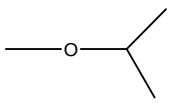
on Bruker Avance 400 spectrophotometer at 400 MHz and the chemical shifts are given as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on PerkinElmer LC-MS PE Sciex API/65. The reactions were monitored by thin layer chromatography (TLC) using silica gel-G (Hexane:Ethyl acetate, 1 : 1). TLC was performed on microscopic slides (2 × 7.5cms) coated with silica-gel-G and pre-coated silica gel 60 F254 strip. Spots were visualized under UV light and by exposure to iodine vapour

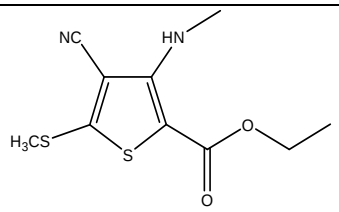
Table 1: Physical data of 2-[(Substituted amino/alkoxy)(methylthio)methylene] malononitriles

(1)



Mobile phase: Ethyl acetate:Hexane= 1:1

Com No.	**R**	**Mol. formula**	**Mol. Wt.**	**% Yield**	**Mel. point (°C)**	**R_f***
1a		$C_{10}H_{13}N_3O_2S$	239.07	25	180-183	0.47
1b		$C_{12}H_{17}N_3O_2S$	267.1	30	185-190	0.55
1c		$C_{15}H_{12}F_3N_3O_2S$	355.09	10	220-222	0.57
1d		$C_{15}H_{12}F_3N_3O_2S$	355.09	15	225-230	0.48
1e		$C_{11}H_{14}N_2O_3S$	254.07	12	150-155	0.49

1f		$C_{17}H_{16}N_4O_4S_3$	36.53	52.3	215-217	0.42

Synthesis of 2-(bis(methylthio)methylene)malononitrile (3)

A 250mL iodine flask was charged with potassium hydroxide (13g, 244mmol) in 10mL water. Malononitrile(6.8g, 102.9mmol) was added in potassium hydroxide in cooling condition. The reaction mixture was strirred for about 10min until salt of malononitrile is formed maintaining temperature. The salt obtained was dissolved in 25ml dimethyl formamide. Carbon disulphide (7.32g, 95.92mmol) was added drop wise using dropping funnel. The reaction mixture was stirred for about 30min. dimethylsulphate (37.71g, 294mmol) was added drop wise using dropping funnel maintaining temperature 0-5˚c. The reaction mixture was stirred for 15min. Light yellow colored solid mass formed which was filtered under vacuum and washed with water. White colored solid obtained as 2-(bis(methylthio) methylene)malononitrile **(123)** (15g, 85.51%) which was pure on thin layer chromatography showing single spot.

Synthesis of 2-[(substituted amino or alkoxy)(methylthio)methylene]malononitrile (4)

2-[(Substitutedamino or alkoxy)(methylthio) methylene] malononitriles **(4)** were synthesized from 2-(bis(methylthio)methylene)malononitrile **(3)** by nucleophilic substitution reaction in which one of thiomethyl groups was displaced by substituted amine or alkoxide. 2-(bis(methylthio)methylene)malononitrile **(3)** was treated with aliphatic amine or sodium salt of alkoxide in presence of isopropranol under stirring for 3 h at room temperature.

Synthesis of ethyl 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate (5)

A mixture of 2-[bis(methylthio)methylene]malononitrile **(3)** (1.7g, 10mmol), potassium carbonate (0.2 g, 1.4 mmol), 15mL acetone, ethyl thioglycolate (1.2g, 10 mmol) was refluxed for 30 min. Reaction mixture was allowed to cool to room temperature and poured in ice cold water. Solid thus obtained was filtered and washed with water and dried. Recrystallization from isopropylalcohol yielded ethyl 3-amino-4-cyano-5-(methylthio)thiophen-2-carboxylate **(5)** (1.5g, 61.98%) as colorless crystalline compound.

Synthesis ethyl 3-amino-4-cyano-5-(dimethylamino) thiophene-2-carboxylate (1a)

A mixture of 2-[(dimethylamino)(methylthio) methylene]malononitrile **(4a)** (1g, 5.9 mmol), potassium carbonate (0.2 g, 1.4 mmol) and ethyl thioglycolate (0.71g, 5 mmol) in 15 ml acetone was refluxed for 1 h. Reaction mixture was cooled to room temperature and the poured in ice cold water. Solid thus obtained was filtered and washed with water and dried. ethyl-3-amino-4-cyano-5-(dimethylamino)thiophen-2-carboxylate **(1a)** (0.25g, 25%) was obtained as colorless crystalline compound. Mass spectrum (in methanol) (m/z): 239.9 (M + 1), 237.9 (M-1) I.R (in KBr, cm-1): 1660 (C=Ostr) 2198 (C≡N str), 3440, 3330 (NH_2 str 1°amine) 1H NMR (DMSO-d6, 400 MHz): 1.2 (t, 3H, $COOCH_2C\underline{H}_3$), 3.2 (s, 6H,-$N(C\underline{H}_3)_2$), 4.4 (q,2H, $COOC\underline{H}_2CH_3$), 6.4 (s, 2H, $N\underline{H}_2$) (D_2O exchangeble)

Synthesis ethyl 3-amino-4-cyano-5-(diethylamino)thiophene-2-carboxylate (1b)

A mixture of 2-[(diethylamino)(methylthio) methylene]malononitrile **(4b)** (1g, 5.84 mmol), potassium carbonate (0.2 g, 1.4 mmol) and ethyl thioglycolate (0.71 g, 5.8 mmol) in 15 ml acetone was refluxed for 1h. Reaction mixture was cooled to room temperature and the poured in ice cold water. Solid thus obtained was

filtered and washed with water and dried. Ethyl-3-amino-4-cyano-5-(diethylamino) thiophen-2-carboxylate **(1b)** (0.4g, 30%) was obtained as colorless crystalline compound. Mass spectrum (in methanol) (m/z): 267.8 (M + 1), 265.8 (M-1) I.R (in KBr, cm-1): 1660 (C=O str), 2196 (C≡N str), 2975 (C-H str), 3419, 3323 (NH_2 str 1° amine). 1H NMR (DMSO-d6, 400 MHz): 0.98-1.4 (m, 9H, $COOCH_2C\underline{H}_3$, -N-$(CH_2C\underline{H}_3)_2$), 3.6 (q, 4H, N-$(C\underline{H}_2CH_3)_2$)), 4.2 (q, 2H, $COOC\underline{H}_2CH_3$), 6.4 (s, 2H, $N\underline{H}_2$), (D_2O exchangeble).

Synthesis of ethyl 3-amino-4-cyano-5-(3-(trifluoromethyl)phenylamino)thiophene-2-carboxylate (1c)

A mixture of 2-[methylthio(3-trifluoromethyl)phenylaminomethylene]malononitrile **(4c)** (0.78 g, 2.7 mmol), potassium carbonate (0.2 g, 1.4 mmol) and ethyl thioglycolate (0.33 g, 2.7 mmol) in 15 ml acetone was refluxed for 1 h. Reaction mixture was cooled to room temperature and the poured in ice cold water. Solid thus obtained was filtered and washed with water and dried. 3-amino-4-cyano-5-(3-(trifluoromethyl)phenylamino)thiophen-2-carboxylate **(1c)** (0.4 g, 15%) was obtained as colorless crystalline compound. Mass spectrum (in methanol) (m/z): 355.9 (M + 1), 353.9 (M-1) I.R (in KBr, cm-1): 1658(C=Ostr) 2208 (C≡N str), 3319, 3283 (NH_2 str, 1° amine), 3415 (N-H str, 2° amine), 1H NMR (DMSO-d6, 400 MHz): δ 6.9 (d, 1H, Ar-H), δ 7.1-7.4 (m, 8H, Ar-H), δ 7.6-7.8 (m, 5H, Ar-H), δ 7.9 (t, 1H, Ar-H), 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H),δ 11.7 (s,1H, NHCO), δ 4.8 (s, 2H, CH2), δ 2.5 (s, 3H, CH3)

Synthesis of ethyl 3-amino-4-cyano-5-(4-(trifluoromethyl)phenylamino) thiophene-2-carboxylate (1d)

A mixture of 2-[methylthio(4-trifluoromethyl) phenylaminomethylene] malononitrile **(4d)** (0.85g, 3mmol), potassium carbonate (0.2 g, 1.4 mmol) and ethyl thioglycolate (0.36 g, 3 mmol) in 15 ml acetone was refluxed for 1 h. Reaction mixture was cooled to room temperature and the poured in ice cold water. Solid obtained was filtered and washed with water and dried. 3-amino-4-cyano-5-(4-(trifluoromethyl)phenylamino) thiophen-2-carboxylate **(1d)** (0.37 g, 10%) was obtained as colorless crystalline compound.

Mass spectrum (in methanol) (m/z): 356.0 (M + 1), 354.0 (M-1) I.R (in KBr, cm-1): 1658 (C=O str.), 2208 (C≡N str), 3319, 3283 (NH_2 str, 1° amine), 3415 (N-H str, 2° amine) 1H NMR (DMSO-d6, 400 MHz): 4.2 (q, 2H,$CO_2C\underline{H}_2CH_3$), 1.2 (t, 3H,$CO_2CH_2C\underline{H}_3$) 5.8 (s,2H,$N\underline{H}_2$) (D_2O exchangeble) 7.2-7.9 (m,4H,Ar-$\underline{H}$), 9.4 (s,H,N$\underline{H}$-Ar) (D_2O exchangeble)

Synthesis of ethyl 3-amino-4-cyano-5-isopropoxythiophene-2-carboxylate (1e)

A mixture of [isopropoxy(methylthio)methylene]malononitrile **(4e)** (0.5 g, 2.7 mmol), potassium carbonate (0.2 g, 1.4 mmol) and ethyl thioglycolate (0.3 g, 2.5 mmol) in 15 ml acetone was refluxed for 1 h. Reaction mixture was cooled to room temperature and the poured in ice cold water. Brown colored oily product obtained which was extracted in dichloromethane and charcolized. Evaporation of dichloromethane gave yellow colored ethyl-3-amino-4-cyano-5-isopropoxythiophen-2-carboxylate **(1e)** (0.3 g, 12%).

Mass spectrum (in methanol) (m/z): 256.0 (M + 1), 254.0 (M-1) I.R (in KBr, cm-1): 2221 (C≡N str) 2981 (C-H str) 3647, 3446 (NH_2 str 1° amine). 1H NMR (DMSO-d6, 400 MHz): δ 6.9 (d, 1H, Ar-H), δ 7.1-7.4 (m, 8H, Ar-H), δ 7.6-7.8 (m, 5H, Ar-H), δ 7.9 (t, 1H, Ar-H), 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H),δ 11.7 (s,1H, NHCO), δ 4.8 (s, 2H, CH2), δ 2.5 (s, 3H, CH3)

Synthesis of ethyl 3-[3'-amino-4'-cyano-2'-(ethoxycarbonyl)thiophene-5yl-amino]-4- cyano-5-methylmercaptothiophene-2-carboxylate (1f)

A mixture of 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **(5)** (1g, 4.1 mmol), isopropylamine (0.48 g, 4.1 mmol), potassium carbonate (0.2 g, 1.4 mmol) in 20 mL dimethylformamide was refluxed for 2 h. Reaction mixture was cooled to room temperature and poured in ice cold water. Solid obtained was filtered and washed with water and dried. Recrystallization from ethanol yielded ethyl 3-[3'-amino-4'-cyano-2'-(ethoxycarbonyl)thiophene-5yl-amino]-4-cyano-5methylmercaptothiophen-2-carboxylate **(1f)** (1g, 52.35%) as a crystalline product.

Mass spectrum (in methanol) (m/z): 437.0 (M + 1), 435.0 (M-1) I.R (in KBr, cm-1): 1666 (C=O str), 1670 (C=O str), 2217 (C≡N str), 3244 (N-H str 2° amine), 3444, 3340 (NH_2 str 1° amine),

1H NMR (DMSO-d6, 400 MHz): 1.2 (t, 3H, $COOCH_2C\underline{H_3}$), 1.3 (t, 3H, $COOCH_2C\underline{H_3}$), 2.8 (s, 3H, $SC\underline{H_3}$), 4.2 (q, 2H $COOC\underline{H_2}CH_3$,), 4.4 (q, 2H, $COOC\underline{H_2}CH_3$), 5.8 (s, 2H, $N\underline{H_2}$) (D_2O exchangeble), 8.8 (s, 1H, N<u>H</u>) (D_2O exchangeble)

Synthesis of 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate (5)

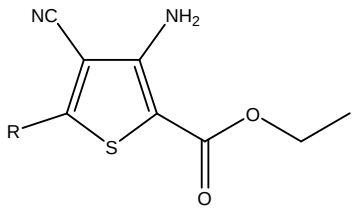
100mL round bottom flask was charged with 2-(bis(methylthio)methylene)malononitrile **(3)** (1.7g, 10mmol), potassium carbonate(0.2g, 1.4mmol), 15mL acetone, ethylthioglycolate (1.2g, 10mmol). Reaction mixture was refluxed for 30min. Reaction mixture was allowed to cool to room temperature and ice cold water was added in reaction mixture. Yellow colored solid crystals was formed which was filtered under vacuum and washed with water and dried. 3-amino-4-cyano-5-(methylthio)thiophene-2-carboxylate **(5)** (1.5g, 61.98%) was recrystallised from isopropylalcohol.

Mass spectrum (in methanol) (m/z): 489 (M + 1), 487 (M-1) I.R (in KBr, cm-1): 3197 (-NH stretching of $CONH_2$), 1710 (C=O stretching of $CONH_2$) 1H NMR (DMSO-d6, 400 MHz): δ 6.9 (d, 1H, Ar-H), δ 7.1-7.4 (m, 8H, Ar-H), δ 7.6-7.8 (m, 5H, Ar-H), δ 7.9 (t, 1H, Ar-H), 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H),δ 11.7 (s,1H, NHCO), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, CH_3)

1. PHARMACOLOGICAL SCREENING

Antiinflammatory Activity (*in vivo*)

All the synthesized compounds were screened for the *in vivo* antiinflammatory activity by carageenan induced rat paw edema method.



(1)

Method:

The method of Winter et al.,[11,12] was employed. Albino wistar rats of either sex (250-300 g) were divided into various groups of three animals each. Animals were deprived of food for 12 h prior to experiment and only water was given *ad libitum.* First group was used as a control and received 1 ml of 0.5 % w/v sodium CMC suspension in saline, the second group received sodium CMC suspension of Ibuprofen (50 mg/kg) orally and the third group received sodium CMC suspension of test compounds at a dose of 50 mg/kg orally. One hour after the administration of the compounds, carageenan suspension (0.1 ml of 1% w/v suspension in 0.9% saline solution) was injected into the sub planter region of left hind paw of the animals. Immediately, the paw volume was measured using plethysmometer (initial paw volume, V_c). Thereafter, the paw volume was measured after 1 and 3 h after carrageenan administration.

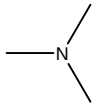
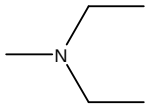
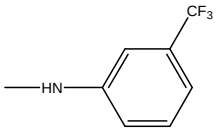
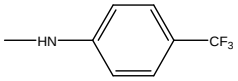
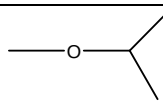
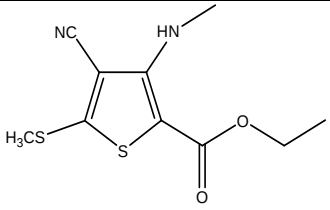
The difference between initial and subsequent readings gave the change in edema volume for the corresponding time. Edema volume of control (V_c) and volume of treated (V_t) were used to calculate percentage (%) inhibition and edema volume (%) by using following formula.

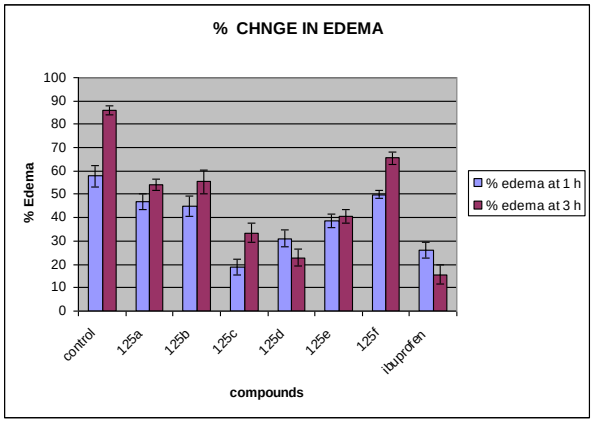
% Inhibition = $[1- (V_t/V_c)] \times 100$

% Edema volume = 100 × (Edema volume after drug treatment/Initial volume

Table 2: Antiinflammatory activity (By rat paw edema method) of ethyl 3-amino-4-cyano-5-(substituted)thiophene-2-carboxylates (1)

Compound No.	R	% Change in Edema (±SEM)	
		1 h	3 h
Control	-----	57.812±4.57	85.93±2.04

Ibuprofen		38.53±3.20	32.40±2.6
1a		44.78±2.9	63.71±2.72
1b		38.43±1.76	67.71±2.72
1c		61.75±3.28	45.87±4.09
1d		56.87±3.6	40.04±2.84
1e		50.13±3.28	55.62±4.16
1f		66.031±3.21	72.62±2.96



RESULTS:

- ❖ All compounds were screened for antiinflammatory activity by inhibition of carageenan induced rat paw edema method at the dose of 50 mg/kg.

❖Significant antiinflammatory activity was observed with inhibition in edema in the range of 26.24 % to 78.30% after 3 h.

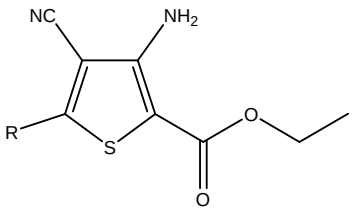
❖ The standard drug Ibuprofen has shown maximum inhibition (81.92%) after 3 h and test drugs also have exhibited maximum inhibition after 3h.

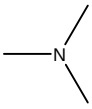
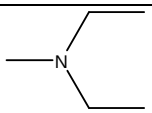
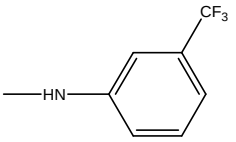
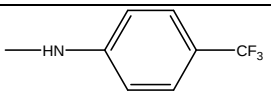
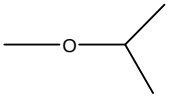
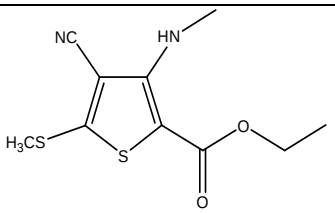
❖ Among all the compounds screened compound **1c** and **1d** were found to be

the most potent in the series with inhibition of 73.24% and 78.30% respectively. standard drug ibuprofen has exhibited % inhibition 81.92%.

❖ Compound 1f was found to be least potent compound in the series with 26.24% inhibition.

Table 3: Antiinflammatory activity (By rat paw edema method) of ethyl 3-amino-4-cyano-5-(substituted)thiophene-2- carboxylates (1)[11,12]



COMPOUND NO.	R	% INHIBITION (±SEM)	
		1 h	**3 h**
Ibuprofen	-----	53.888±3.17	81.92±3.6
1a		16.66±3.609	37.45±3.75
1b		20.55±2.90	36.37±2.84
1c		44.44±4.40	73.24±5.13
1d		47.77±3.28	78.30±4.16
1e		31.66±1.76	53.00±2.72
1f		11.11±2.96	26.24±3.21

Ulcerogenic Potential[159]

Compound 1c emerged out as a potent antiinflammatory agent among the screened compounds. Thus it was thought of interest to evaluate it for ulcerogenic potential, which is considered as the most common side effect associated with NSAIDs.

Method:

The Albino wistar rats of either sex, weighing 200-250 g, were divided into various groups of three animals each. The rats were deprived of food for 36 h before administration of drug. First group was kept as control group, second group received standard drug ibuprofen in form of sodium CMC suspension at a dose of 50 mg/kg. The remaining groups were given test compound **1c** in form of sodium CMC suspension at a dose of 50 mg/kg. After six hours, the animals were sacrificed and stomach was taken out. The stomach was opened along the grater curvature and examined for haemorrhages and ulcers with the help of hand lens and

compared with that of ibuprofen treated group. Ulcer index was calculated using following formula:

Ulcer index = 10/x

Where, x = (Total mucosal area / Total ulcerated area)

Table 4: Ulcerogenic index

Sr. No	Compound	Ulcer index (± SME)
1	Ibuprofen	0.53± 0.07
2	1c	0.45± 1.06

RESULTS:

Ulcer index of the compound **1c** was found to be 0.45 while that of ibuprofen was found to be 0.53. Test compound has shown less ulcerogenic potential than standard drug ibuprofen.

Structure activity relationship

- potent antiinflammatory activity in a series of ethyl 3-amino-4-cyano-5-(substituted)thiophene-2-carboxylates with in the series was observed as 4-triflouromethyl aniline > 3-triflouromethyl aniline > isopropylamine > isopropyloxy > dimethylamine > diethylamine > dimer (1f)
- It can be observed from the result that compound with aromatic ring at 5th position of substituted thiophene of a series shows higher potency than aliphatic substitution.
- Electron withdrawing group at para position in the aromatic ring at 5th position of thiophene has enhanced potency.
- In case of compounds containing aliphatic amine at 5th position of thiophene of series, compound with larger aliphatic amine show good inhibitory activity.
- Small aliphatic amines like dimethylamine and diethylamine decrease activity significantly.
- Alkoxy group at 5th position isopropoxyl exhibits good activity compare to corresponding amine.
- Compound with cyclic aliphatic amine like piperazine, N-methyl piperazine, morpholine and pyrrolidine at 5th position show good inhibitory activity than small aliphatic amine.
- Larger cyclic aliphatic amines increase biological activity and smaller cyclic aliphatic amines decrease biological activity.
- Ulcer index of compound with aromatic amine at 5th position was found 0.45 than the aliphatic group.

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