SYNTHESIS OF SOME 2- SUBSTITUTED AMINO-3-(N-m-TOLYL CARBOXAMIDO) 4, 5 TRIMETHYLENE THIOPHENES FOR ANTI-INFLAMMATORY ACTIVITY

ARCHANA SWAMY. P[1]*, SYED BILAL[1], CHANDANAM SREEDHAR[2] , MOHAN. S[3]
[1]Gautham College of Pharmacy, RT Nagar, Bangalore, Karnataka.
[2]Acharya&B.M.Reddy College of pharmacy, Bangalore.
[3]P.E.S college of Pharmacy, Bangalore, Karnataka

ABSTRACT

The present study was focused on the synthesis of new series of some 2-substituted amino-3-(N-m-Tolyl carboxamido) 4, 5 Trimethylene Thiophenes. The synthesized compounds were evaluated for anti-inflammatory activity.

1.INTRODUCTION

The chemistry of Thiophenes and its derivatives has known over 95 years. The development of Thiophenes and its derivatives have attracted maximum attraction due to their varied physiological and pharmacological properties. Some of these are found to have Thiopene derivatives are known to have a promising anti-inflammatory activity (Goodman,1992; Daries,1992; Tomiyama,1992;Gewald,1989). In the present study, we synthesized, a new class of 2- substituted amino-3 (N-m-tolyl carboxamido) 4, 5- Trimethylene Thiophenes and evaluated for their anti-inflammatory activity.

2.EXPERIMENTAL

Scheme I

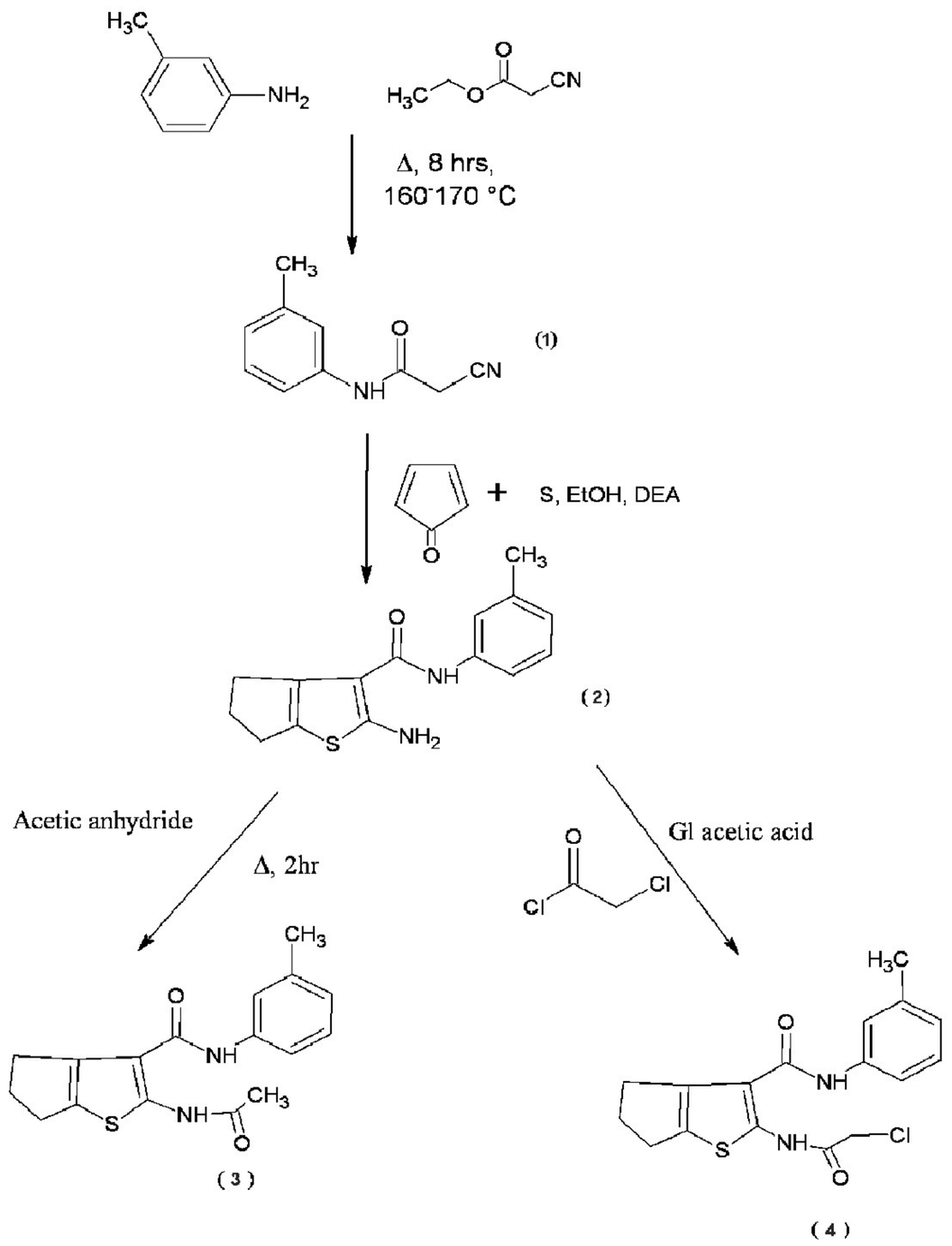
A mixture of m-toludine (107g; 1.0 mole) and ethyl cynoacetate (74g; 0.655 mole) was heated at 160-170^{O}C for 8h and left at room temperature over night. The solid (1) obtained was filtered, washed with ethanol and crystallized from alcohol. (m.p. 130^{O} C, yield 45%).

A mixture of cyclopentanone (3.36ml; 0.04 mole), N-m-tolyl cyanoacetamide(1)(6.96g; 0.04mole), ammonium acetate (1g) and glacial acetic acid(2ml) in benzene(80ml) was refluxed for 10h. The reaction mixture was cooled, diluted with benzene and washed with water. The crude α-(N-m-tolyl carboxamido) alpha pentylidine acetonitrile thus obtained, was further added to sulphur (1.28; 0.04mole) in ethanol (40ml), diethyl amino (4.0ml) drop wise with stirring for 1h at 45-50^{O}C, chilled overnight and the solid obtained was filtered, washed with ethanol and recrystalised from benzene(2)(m.p 123^{O} C, yield 44%).

A mixture of 2(2g) and acetyl anhydride (10ml) was heated on a steam bath for 2h and mixture was cooled. Left over night, the solid obtained was filtered, washed with cold ethanol, recrystalised from a mixture of alcohol and acetone to yield colorless crystalline compound(3) (m.p145^{O} C, yield 59%).

To a suspension of 3(3.12g; 0.0115 mole) in glacial acetic acid (30ml) was added chloroacetyl amide (3.9; 0.035 mole) drop wise at room temperature. The reaction mixture was refluxed for 5h, cooled and poured into water. The crude product was filtered, washed with water and recrystalised from benzene to get a grey color crystallized product (4) (m.p.180^{O} C, yield 76.8%).

SCHEME-1



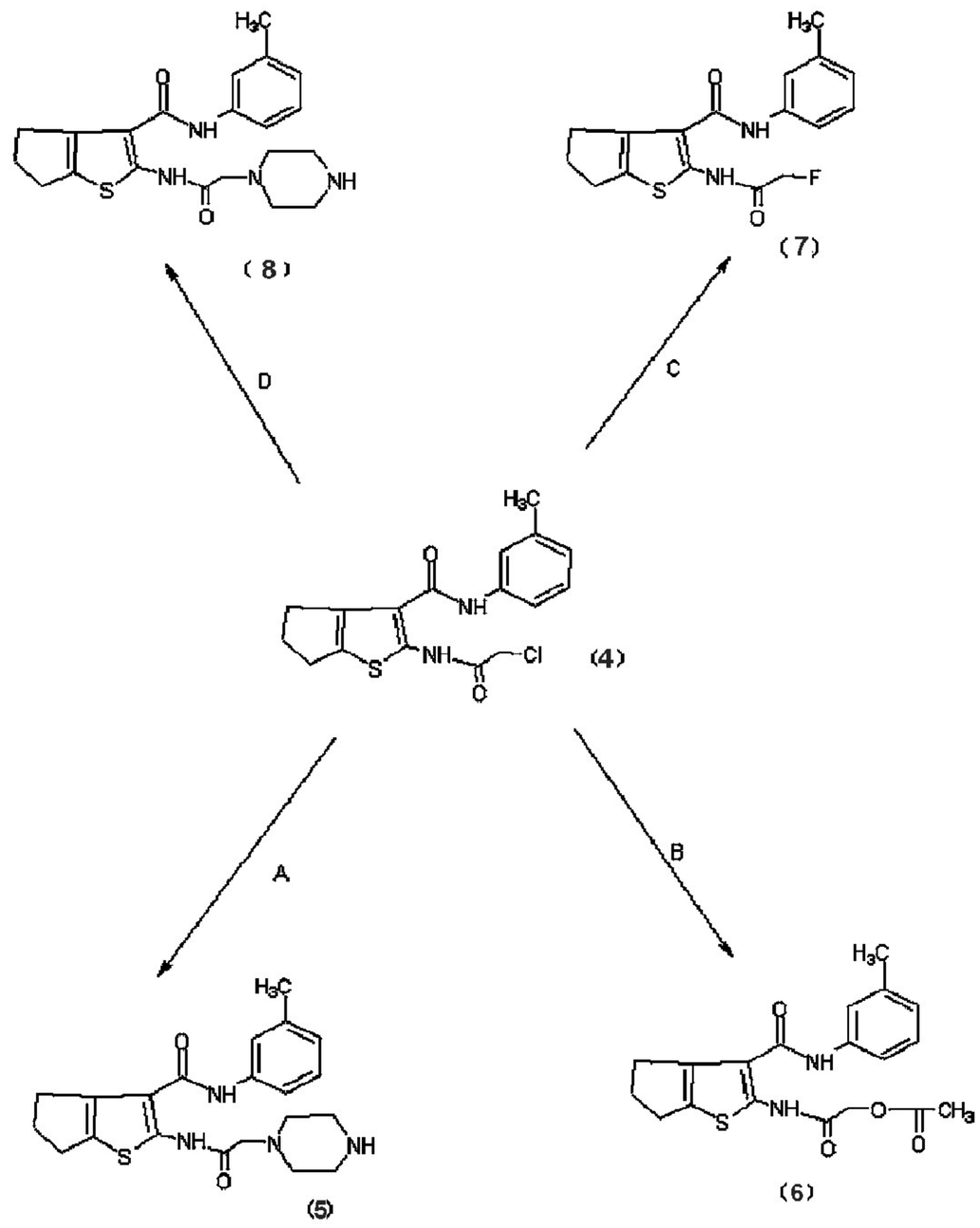
***Corresponding author**
Email:archana_raveesh@rediffmail.com

Comp.	m.p.(^{0}C)	Yield (%)	solvent	m.f.	Characterization data
1	130	45	n-hexane:ethylacetate 4 : 2	$C_{10}H_{10}N_2O$	3273cm^{-1} (s, N-H) 2920cm^{-1}(m, Ar C-H) 2260cm^{-1} (m, CN) 668cm^{-1} (s, C=O)
2	123	44	n-hexane:ethylacetate 4 : 2	$C_{15}H_{16}N_2OS$	3402cm^{-1}(s, NH_2) 3301cm^{-1}(s, NH) 1633cm^{-1}(s, C=O) 1400cm^{-1}(s,Thiophene) 1242cm^{-1}(s,Thiophene)
3	145	59	n-hexane:ethylacetate 4 : 2	$C_{17}H_{18}N_2O_2S$	3433cm^{-1}(s,N-H) 1678 cm^{-1}(s, C=O) 1637cm^{-1}(s, C=C-C=O) 1407cm^{-1}(m,Thiophene) 1232cm^{-1}(s, Thiophene)
4	180	76.8	n-hexane:ethylacetate 4 : 2	$C_{17}H_{17}N_2O_2SCl$	3432cm^{-1}(s, N-H) 1672cm^{-1}(s ,C=O) 1637cm^{-1}(s, C=C-C=O) 1421cm^{-1}(m,Thiophene) 1232cm^{-1}(s, Thiophene) 763cm^{-1} (s, C-Cl)

Scheme 2

The compound 2-substituted-3-(N-m-tolyl carboxamido) 4, 5-trimethylene Thiophenes (5-8) were synthesized by refluxing 3-N-m-tolyl carboxamido-2-(α-choloro acetamido) 4, 5- Trimethylene thiophene (0.005mole) (4) with morpholine (0.015mole) in benzene (30ml), potassium acetate (0.07mole) in glacial acetic acid(75ml), potassium fluoride(0.015mole) in ethanol (40ml) and anhydrous piprazine (0.015mole) in benzene(30ml) for 8h respectively. The reaction mixture was cooled, poured into ice-water. The separated solid collected by filtration and crystallized from suitable solvent.

SCHEME-2



Comp.	m.p. ^{o}C	Yield(%	solvent	m.f.	Characterization data
5	168	75	n-hexane:ethylacetate 4 : 2	$C_{21}H_{25}N3O_3S$	3435cm^{-1}(m, N-H) 1680cm^{-1}(m, C=O) 1643cm^{-1}(m, C=C-C=O) 1485cm^{-1}(m, Thiophene) 1251cm^{-1}(m, Thiophene
6	128	70.2	n-hexane:ethylacetate 4 : 2	$C_{19}H_{20}N_2O_4S$	3429cm^{-1} (m, N-H) 1757cm^{-1} (m, OCO-CH_3) 1670cm^{-1}(m, C=O) 1637cm^{-1}(s, C=C-C=O) 1487cm^{-1}(m, Thiophene) 1228cm^{-1}(m, Thiophene)
7	148	62.5	n-hexane:ethylacetate 4 : 2	$C_{17}H_{17}N_2O_2F$	3430cm^{-1}(w, W-H) 1676cm^{-1}(s, C=O) 1643cm^{-1}(m, C=C-C=O) 1485cm^{-1}(m, Thiophene) 1201cm^{-1}(m, Thiophene) 1037cm^{-1}(w, C-H)
8	130	63	n-hexane:ethylacetate 4 : 2	$C_{21}H_{26}N_4O_2S$	3435cm^{-1}(m,,N-H) 1679cm^{-1}(s, C=O) 1645cm^{-1}(s,C=C-C=O) 1413cm^{-1}(m,Thiophene) 1217cm^{-1}(s, Thiophene)

ANTI-INFLAMMATORY ACTIVITY

The synthesized compounds were tested for their anti-inflammatory activity using carrageenin induced rat hind paw oedema method.

Comp.	Chemical name	Anti-inflammatory activity		Level of significance
		Mean vol (ml±S.E)	% inhibition	
3	2-acetyl amino-3-(N-M-tolyl carboxamido)4,5 Trimethylene thiophene	0.32±0.037	50%	P<0.001
4	3-N-m-tolyl2-(w-chloro acetamido)4,5 Trimethylene thiophene	0.26±0.040	60%	P<0.001
5	2-w-Morpholino acetamido 3-N-mtolyl carboxamido 4,5 Trimethylene thiophene	0.28±0.037	57%	P<0.001
6	2-w-acetoxy acetoxide-3(N-M-toyl carboxamido)4,5 Trimethylene thiophene	0.32±0.037	50%	P<0.001
7	2-w-fiouro acetamido 3-(N-m-tolyl carboxamido)4,5 Trimethylene thiophene	0.2±0.0316	66%	P<0.001
8	2-w-piperazino acetamido 3-(N-M-tolyl carboxamido)4,5 Trimethylene thiophene	0.34±0.002	47%	P<0.001
	Standard-(Diclofenac sodium)	0.16±0.24	75%	P<0.001
	Control (Tween 80)	0.64±0.0024	–	–

The compounds 4 and 7 showed good activity (60% and 66%) and the remaining compounds 3, 5, 6 and 8 showed considerable anti-inflammatory activity.

3.ACKNOWLEDGEMENT

The authors are thankful to the management, Gautham college of pharmacy, Bangalore for providing facilities.

REFERENCES

Daries V, Bravo L, Abdallaha S.S, Sandez, Mateo C, Arch.Pharm.Weinheim Ger., 325 (2), 1992, 83-7, Chem.Abstr., 116, 1992, 151468y.

Gewald Karl, Schaefer, Harry, Bellmann peter, Chem.Abstr., 111, 1989, 115019r.

Goodman, Mark M, Kabalka, George w, Marks, Ronald C, J.Med.Chem., 35 (2), 1992, 280-5, (Eng), Chem.Abstr., 116, 1992, 59127p.

Tomiyama Takeshi, Tomiyama Itaru, Wakabayashi, Shuchi, Mochizuki, Seichiro, Fatamura Masayaki, Chem.Abstr., 116, 1992, 15155z.