Asian Journal of Chemistry Vol. 19, No. 5 (2007), 3541-3544

Synthesis and Antiinflammatory Evaluation of Some New Thiophene Analogs

KUNTAL HAZRA*, J. SARAVANAN and S. MOHAN
Department of Pharmaceutical Chemistry, PES College of Pharmacy
BSK-Ist Stage, Hanumanthnagar, Bangalore-560 050, India
E-mail: kuntal252003@yahoo.co.in

The synthesis of 2-amino-3-carboxyanilido-6-N-methyl piperidino thiophene (**2**) was synthesized *via* a multicomponent condensation between sulphur, N-methylpiperdin-4-one and cyanoacetanilide adapting Gewald reaction. It was condensed with different substituted aryl aldehydes to yield 10 thiophene analogs (**3a-j**). Later **2** was reacted with acetic anhydride and chloroacetylchloride to form **4** and **5**. Finally compound **5** was reacted with morpholine and piperazine anhydrous to form **6** and **7**. The compounds were characterized by spectral data and were subjected to antiinflammatory activity.

Key Words: Synthesis, Antiinflammatory activity, Gewald reaction.

INTRODUCTION

A number of thiophenes and Schiff bases[1-4] were reported to possess different biological activities like antitubercular, antifungal, analgesic, anti-inflammatory activities. These findings prompted us to synthesize some 2-amino-3-carboxyanilido-6-N-methyl piperidino thiophene (**2**) analogs.

EXPERIMENTAL

Melting points are uncorrected and IR (KBr) was recorded on Perkin Elemer spectrum RX_1. ^1H NMR spectra were recorded on Bruker-Avance 700 MHz and the chemical shift values are in δ (ppm), Maldi MS was used to record mass spectra.

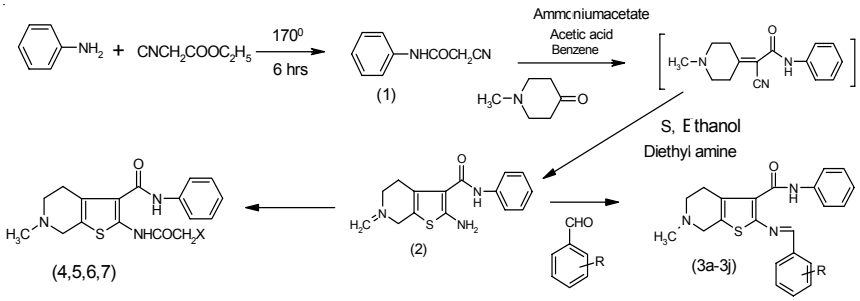
2-amino-3-carboxyanilido-6-N-methyl piperidino thiophene (2): The initial compound cyanoacetanilide (**1**) was prepared by heating aniline (94 mL, 1 mol) and ethylcyanoacetate (70 mL, 0.625 mol) at 170ºC for 6 h. The cyanoacetanilide (6.4 g, 0.04 mol) was refluxed with N-methyl piperidin-4-one (4.65 mL, 0.04 mol) with an arrangement for continuous separation of water by Dean-stark apparatus for 8 h. The intermediate so formed was immediately cyclized by using sulphur in alkaline medium to yield the compound **2**. The product was crystallized from benzene.

General method for the synthesis of schiff bases (3a-j): 2-Amino-3-carboxanilido-6-N-methyl piperidino thiophene (0.0075 mol) and substituted aryl aldehyde (0.0075 mol) was taken in 30 mL of ethanol and catalytic amount of glacial acetic acid (2-3 drops), the reaction mixture was refluxed for 2 h. The solid obtained was filtered washed with ethanol, dried and recrystallized from DMF:water (5:1).

2-Acetyl amino-3-carboxanilido-6-N-methyl piperidino thiophene (4): A mixture of 2-amino-3-carboxanilido-6-N-methyl piperidino thiophene (1.69 g, 0.0075 mol) and acetic anhydride (10 mL) was heated on a steam bath for 2 h (30 s under microwave irradiation) and the mixture was cooled to room temperature and left overnight. The solid obtained was filtered, washed with cold ethanol and recrystallized from ethanol.

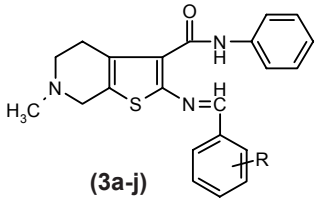
2-(2-ω chloroacetamido)-3-carboxanilido-6-N-methyl piperidino thiophene (5): To a suspension of 2-amino-3-carboxanilido-6-N-methyl piperidino thiophene (4.485 g, 0.015 mol) in glacial acetic acid (30 mL) was added chloroacetyl chloride (3.95 g, 0.035 mol) drop wise at room temperature. Then the reaction mixture was refluxed gently on wire gauze for 5 h, cooled and poured into ice cold water. The crude product was filtered and crystallized using DMF:water (5:1).

2-(2-morpholino/piperazine acetamido)-3-carboxanilido-6-N-methyl piperidino thiophene (6): To a suspension of 2-(2-ω chloroacetamido)-3-carboxanilido-6-N-methyl piperidino thiophene (4.485 g, 0.015 mol) and morpholine/piperazine (0.0155 mol) in benzene (30 mL) was refluxed for 8 h. The solvent was removed under vacuum. The oily residue was cooled and triturated with cold water. The solid obtained was filtered and crystallized using DMF:water (5:1).

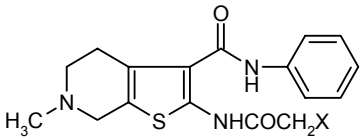


SCHEME

All the synthesized compounds (**3a-j**), **4, 5, 6, 7** were screened for their *in vitro* and *in vivo* antiinflammatory activity by inhibition of bovine serum albumin denaturation[5] and Carrageenin induced rat hind paw edema method[6] respectively using Ibuprofen as a standard drug.



(3a-j)



(4-7)

TABLE

S. No.	Comp No	X/R	Inhibition (%)	
			in vitro	*in vivo*
1	3a	4-Hydroxy phenyl	46.72	42.80
2	3b	2-Nitro phenyl	24.02	38.20
3	3c	3-Nitro phenyl	26.22	32.00
4	3d	2-Hydroxy phenyl	48.00	46.32
5	3e	2-Chlorophenyl	53.22	48.50
6	3f	4-Hydroxy-3-methoxy phenyl	28.27	34.10
7	3g	4-Methoxy phenyl	28.00	36.02
8	3h	3,4-Dimethoxy phenyl	30.22	38.02
9	3i	4-Dimethyl amino phenyl	32.20	36.20
10	3j	3,4,5-Trimethoxy phenyl	34.32	40.62
11	4	-H	68.21	68.60
12	5	-Cl	61.46	50.90
13	6	Morpholinyl	65.04	62.00
14	7	Piperazinyl	66.02	66.20
15	Ibuprofen		68.67	74.00

RESULTS AND DISCUSSION

All the Schiff bases are bright coloured solids. The formation of cyanoacetanilide (**1**) was confirmed by the presence of specific IR peaks at 2360 cm^{-1} (C≡N), 3272 (NH), 1690 (C=O); 2918 (s) (CH_3); 2872 (s) (CH_2).

The formation of 2-amino-3-carboxanilido-6-N-methyl piperidino thiophene (**2**) was confirmed by the presence of specific IR peaks at 3339.61 (NH); 1653 (CO); 2933 (s) (CH_3); 2795 (s) (CH_2); 1250 (C-S); 1051 (C-N).

Mass spectra of 1c recorded in Maldi MS showed m/z peak at 286.8: The formation and purity of the new Schiff bases (**3a-j**) were confirmed by the difference in m.p., R_f values and specific IR peaks. ^{1}H NMR spectra of the following compounds.

3c = 10.73 (s, 1H, NH), 8.83 (s, 1H, CH), 8.53 (s, 1H, N=CH), 8.38 (d, 1H, CH), 8.10 (d, 1H, CH), 7.80 (d, 2H, CH), 7.75 (t, 1H, CH), 7.40 (t, 2H, CH), 7.15 (t, 1H, CH), 3.63 (s, 2H, CH_2), 3.25 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 2.5 (s, 3H, N-CH_3 methylenic protons of N-methylpiperidin-4-one).

3g = 11.14 (S, 1H, NH), 8.38 (s, 1H, CH), 7.85 (d, 2H, CH), 7.70 (d, 2H, CH), 7.35 (t, 2H, CH), 7.11 (t, 1H, CH), 7.02 (d, 2H, CH), 3.9 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2), 3.23 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 2.49 (s, 3H, N-CH_3 methylenic protons of N-methyl piperidin-4-one).

3i = 11.42 (s, 1H, NH), 8.30 (s, 1H, CH), 7.79 (d, 2H, CH), 7.72 (d, 2H, CH), 7.35 (t, 2H, CH), 7.08 (t, 1H, CH), 6.76 (d, 2H, CH), 3.57 (s, 2H, CH_2), 3.23 (t, 2H, CH_2), 2.73 (t, 2H, CH_2), 3.11 (s, 6H, $N(CH_3)2$), 2.48 (s, 3H, N-CH_3 methylenic protons of N-methyl piperidin-4-one).

5 = 12.98 (s, 1H, NH), 7.7 (s, 1H, CH), 7.57 (d, 2H, CH), 7.23 (t, 2H, CH), 7.0 (t, 1H, CH), 4.7 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 3.9 (t, 2H, CH_2), 3.3 (t, 2H, CH_2), 2.85 (s, 3H, N-CH_3 methylenic protons of N-methyl piperidin-4-one).

Finally, out of 14 compounds screened for antiinflammatory activity, compound 4 showed considerable antiinflammatory activity, in both *in vitro* and *in vivo* method compared to the standard.

REFERENCES

1. J. Saravanan and S. Mohan, *Indian J. Heterocycl. Chem.*, **7**, 285 (1998).
2. J. Saravanan, S. Mohan and Nargund, *Indian J. Heterocycl. Chem.*, **6**, 203 (1997).
3. V.S. Raju, S. Mohan and J. Saravanan, *Indian J. Heterocycl. Chem.*, **8**, 59 (1998).
4. P. Govindswamy, S. Mohan and J. Saravanan, *Indian J. Heterocycl. Chem.*, **7**, 205 (1998).
5. G. Elias and M.N.A. Rao, *Indian J. Experiment. Bio.*, **26**, 540 (1988).
6. L.C. Miller and M.L. Tainter, *Proc. Soc. Exp. Therap.*, **128**, 82 (1944); R.A. Turner, Screening Methods in Pharmacology. Academic Press, London (1965).

(*Received*: 14 March 2006; *Accepted*: 24 February 2007) AJC-5444