WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 1838-1849. Research Article ISSN 2277– 7105

SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC SCREENING OF SOME NEW BENZOTHIOPHENE DERIVATIVES

H. J. Kallur*, Prabhudev S. Mathapati, Kishore Singh C. and Ashok Malpani

Department of Pharmaceutical Chemistry, R.M.E.S's College of Pharmacy, Balaji Nagar, Old Jewargi Road, Kalaburagi-585102, Karnataka, India.

Article Received on
15 March 2020,
Revised on 05 April 2020,
Accepted on 26 April 2020
DOI: 10.20959/wjpr20205-17450

***Corresponding Author**
Dr. H. J. Kallur
Department of
Pharmaceutical Chemistry,
R.M.E.S's College of
Pharmacy, Balaji Nagar, Old
Jewargi Road, Kalaburagi-
585102, Karnataka, India.

ABSRACT

The proposed work was carried out by following Schemes. In the Scheme-I the starting material cinnamic acid was reacted with thionyl chloride, in presence of pyridine in chlorobenzene medium to yield 3-chlorobenzo[b]thiophene-2-carbonylchloride (1). Where as in the Scheme-II the 2-amino-6-substituted benzothiazole is prepared by the reaction of 4-substituted aniline and potassium thiocyanate in presence of bromine in acetic acid. In the scheme-III the compound *N*-(6-substituted-1,3-benzothiazol-2-yl)-3-chloro-1-benzothiophene-2-carboxamide (3a-f) was prepared by reacting 3-chlorobenzo[b] thiophene-2-carbonylchloride (1) and 2-amino-6-substituted benzothiazole (2) / 2-amino substituted pyridine in pyridine medium refluxed for 10-15 h furnished title compound *N*-(6-Substituted-1,3-benzothiazol-2-yl)-3-chloro-1- benzothiophene-2-carboxamide (3a-f). The structures of the all synthesized compounds were characterized by their spectral data like ^{1}H NMR, Mass and IR Spectra. The synthesized compounds were evaluated for the anthelmintic activity.

KEYWORDS: Benzothiophene, Synthesis, Characterization, anthelmintic activity.

INTRODUCTION

The drug design by molecular manipulation is a productive source of new drugs. The biological study of natural products with medicinally useful property and some of the derivatives and analogues furnish the early 'Lead' about the possible relation of chemical structure and overall biological behavior of the compound. Further, it soon became evident that certain structural groups present in the natural products were present in other compounds having same biological activity and this observation was a guiding thought in the present work in exploring the synthesis of some new benzothiophene compounds with a desire to obtain highly potent, more specific and less toxic drugs. Combination of two or more active moieties into one is a common procedure of manipulation and this can possibly results in augmenting the activity, removal of untoward side effects and particularly prevent the development of resistance by the infectious micro-organisms.

By considering the above facts we plan to synthesize a biheterocyclic system comprising of benzothiophene nucleus and biologically important heterocyclic system like benzothiazole moiety. We have also planned to evaluate the synthesized compounds for anthelmintic activity.

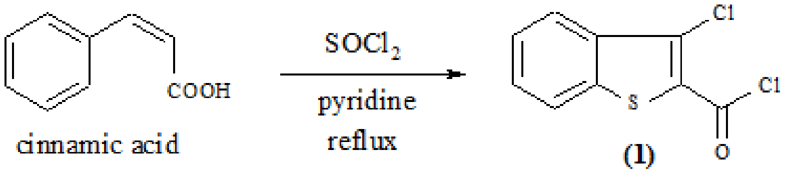
MATERIALS AND METHODS

All reagents and solvents used were of analytical grade have been purchased from S. D. Fine. Chem. Ltd. Mumbai, India & sigma-Aldrich. Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using Methanol: Chloroform (7:3) solvent system and U.V lamp used as a visualizing agent. IR spectra were recorded using KBr pellets on a JASCO FT/IR-5300 spectrophotometer. ^{1}H-NMR spectra on a Varian EM-200 spectrophotometer using DMSO and $CDCl_3$ solvent and TMS as internal standard (chemical shift values expressed in δ ppm). Mass spectra were recorded by LCMS technique.

EXPERIMENTAL

1. Synthesis of 3-chlorobenzo[b]thiophene-2-carbonylchloride (1)

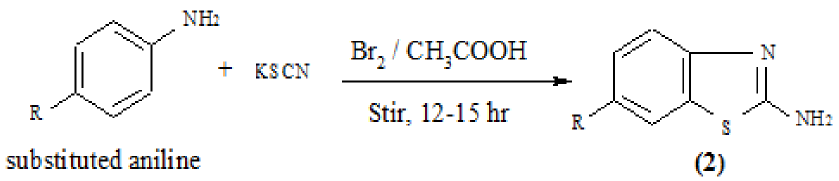
SCHEME-I



A stirred mixture of cinnamic acid (0.5 mol), pyridine (0.05 mol), thionyl chloride (0.77 mol) and chlorobenzene (300 ml) was heated at reflux for 48 hr. excess of thionyl chloride was removed under reduced pressure and the remaining material was suspended in hot hexane (800 ml) the filtered. The hot filtrate was treated with charcoal, filtered and allows cooling; the obtained precipitate was collected as yellow needled, m.p. 114-116°C.

2. Synthesis of 2-amino-6-substituted benzothiazole (2)

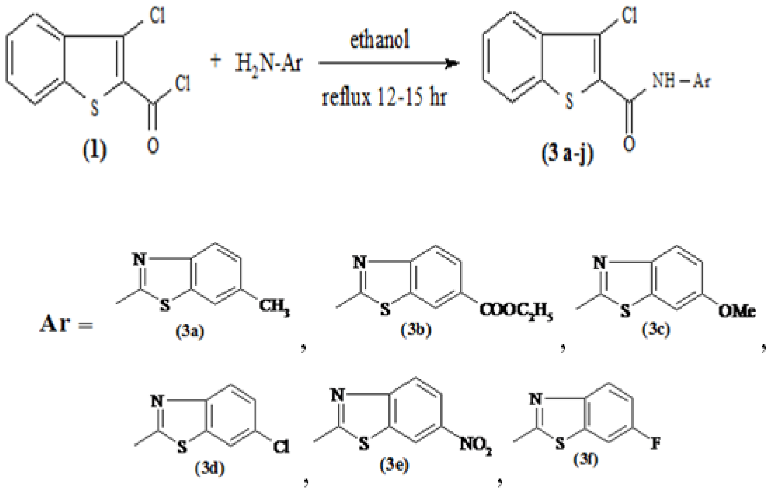
SCHEME-II



To a solution of 4-substituted aniline (0.2 mol) and potassium thiocyanate (0.8 mol) in acetic acid (360 ml) added drop wise with stirring a solution of bromine (0.2 mol) dissolved in acetic acid (150 ml) by maintaining the temperature 30 ^{o}C by keeping in ice bath. After all the bromine solution added the mixture was stirred for 10-15 h, the mixture was filtered neutralized with aq ammonia solution. The obtained precipitate was filtered washed with water and dried. The crude product was recrystallized with suitable solvents. The physical data was presented in the Table No 1.

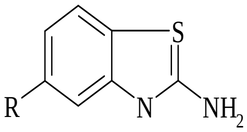
3. Synthesis of *N*-(6-Substituted-1,3-benzothiazol-2-yl)-3-chloro-1-benzothiophene-2-carboxamide (3 a-f)

SCHEME-III



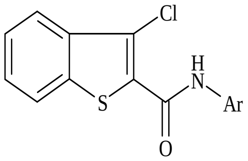
The compound 3-chlorobenzo[b]thiophene-2-carbonylchloride **(1)** (0.002 mol) and 2-amino-6-substituted benzothiazole **(2)** / 2-aryl substituted amine (0.002 mol) dissolved in 25-30 ml of pyridine and refluxed for 10-15 h. The reaction mixture was cooled and poured into the ice cooled water. The solid separated was filtered washed with water, dried. The crude product was recrystallized from ethanol. The physical data was presented in the Table No 2.

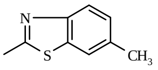
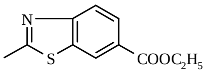
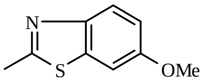
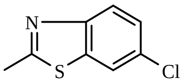
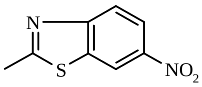
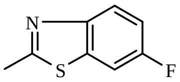
Table No 1: Physical Characterization Data of Synthesized Compounds 2.



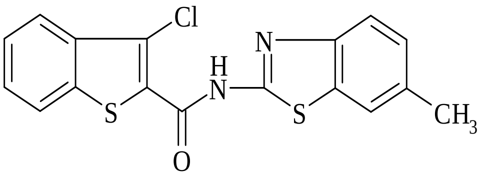
R	Molecular Formula	Molecular Weight	Melting point(^{0}C)	Yield (%)
CH_3	$C_8H_8N_2S$	164	206	52
$COOC_2H_5$	$C_{10}H_{10}N_2O_2S$	222	230	58
OCH_3	$C_8H_8N_2OS$	180	236	55
Cl	$C_7H_5N_2SCl$	184	210	59
NO_2	$C_7H_5N_3O_2S$	195	240	51
F	$C_7H_5N_2SF$	168	216	57

Table No 2: Physical characterization data of synthesized compounds 3(a-f).



Compound Code	Ar	Molecular Formula	Molecular Weight	Melting Point (^{o}C)	Yield (%)
3a		$C_{17}H_{11}N_2OS_2Cl$	258	220	54
3b		$C_{19}H_{13}N_2O_3S_2Cl$	416	240	52
3c		$C_{17}H_{11}N_2O_2S_2Cl$	374	208	56
3d		$C_{16}H_8N_2OS_2Cl_2$	379	220	50
3e		$C_{16}H_8N_3O_3S_2Cl$	389	230	53
3f		$C_{16}H_8N_2OS_2ClF$	362	226	58

SPECTRAL INTERPRETATION



3-chloro-*N*-(6-methyl-1,3-benzothiazol-2-yl)-1-benzothiophene-2-carboxamide

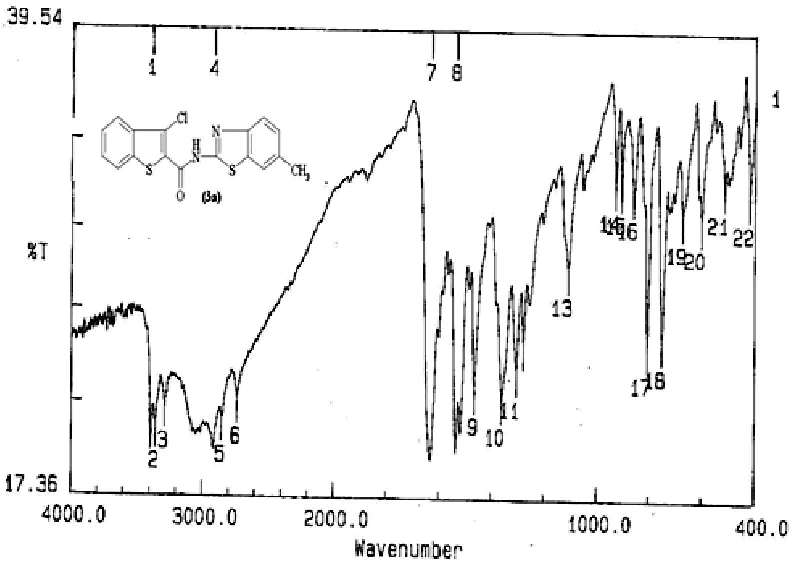


Figure No 1: IR Spectra of Compound 3a.

IR (KBr cm^{-1}): Absorption band appears at 754 and 862 substituted benzene, 1638 C=O, 2856 and 2918 Ar-CH stretching, 3288, 3360 and 3395 NH stretching.

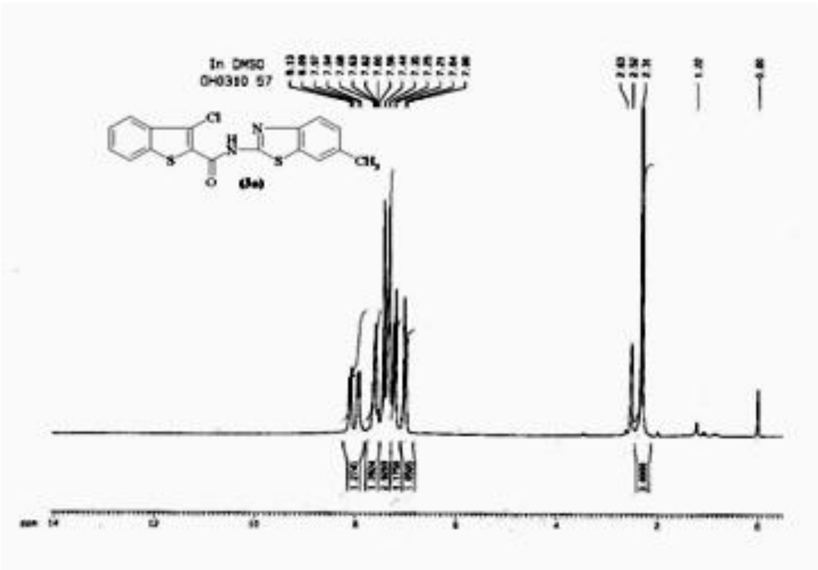


Figure No 2: ^{1}H NMR Spectra of Compound 3a.

^{1}H NMR (DMSO, δ ppm): 2.3 to 2.4 (3H, s, 3H of CH_3), 7.0 to 8.1 (8H, m, 7H of Ar-H and 1H of CONH).

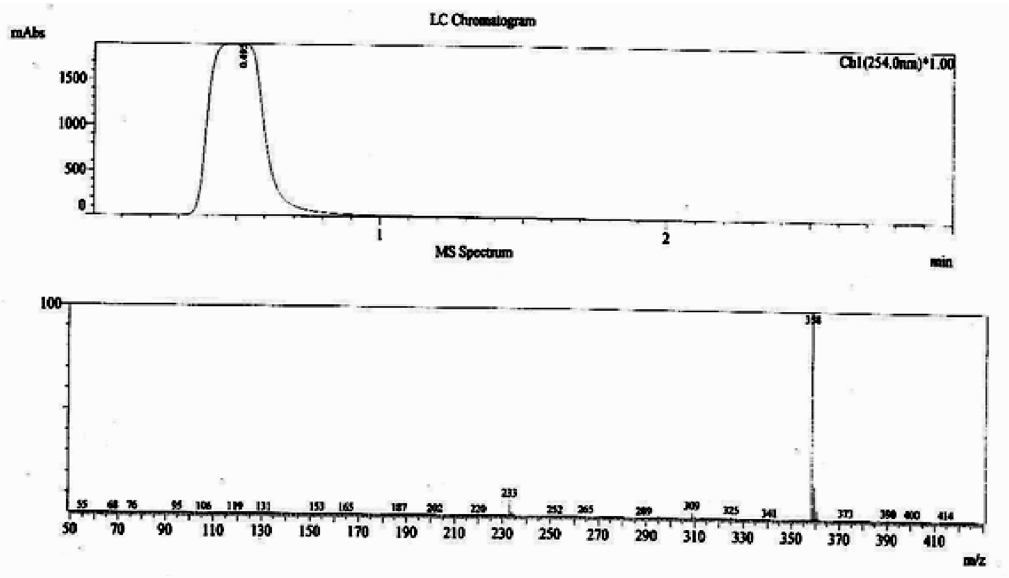


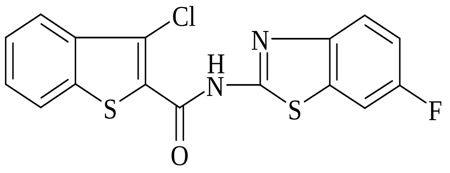
Figure No 3: Mass Spectra of Compound 3a.

LCMS (m/z): Molecular ion peak appear at 358 as (M+).

Mol. Formula: $C_{17}H_{11}N_2OS_2Cl$.

Mol. Wt. : 358

Melting Point: 220 °C



3-chloro-*N*-(6-fluoro-1,3-benzothiazol-2-yl)-1-benzothiophene-2-carboxamide

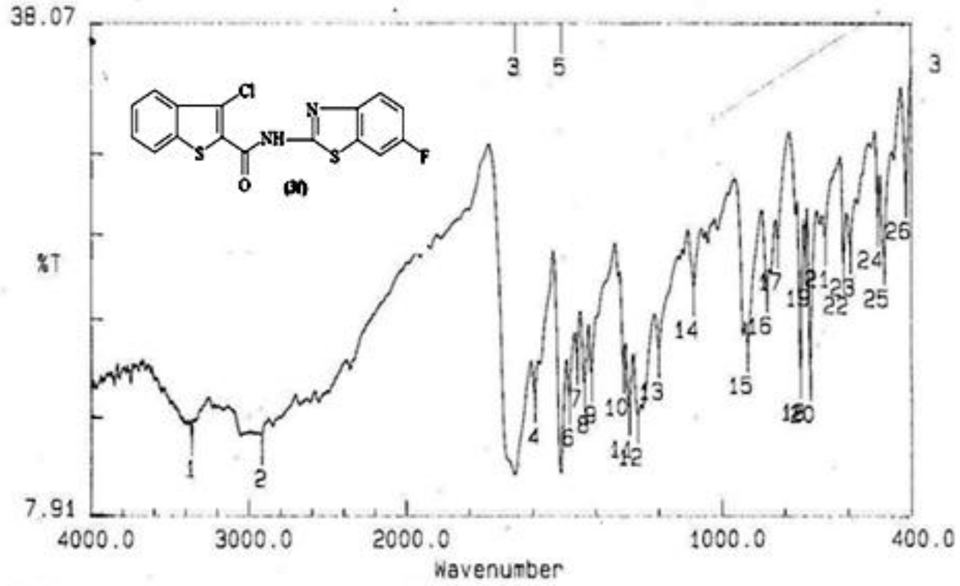


Figure No 4: IR Spectra of Compound 3f.

IR (KBr cm^{-1}): Absorption band appears at 752 and 858 substituted benzene, 1657 C=O, 2820 and 2918 Ar-CH stretching, 3366 NH stretching.

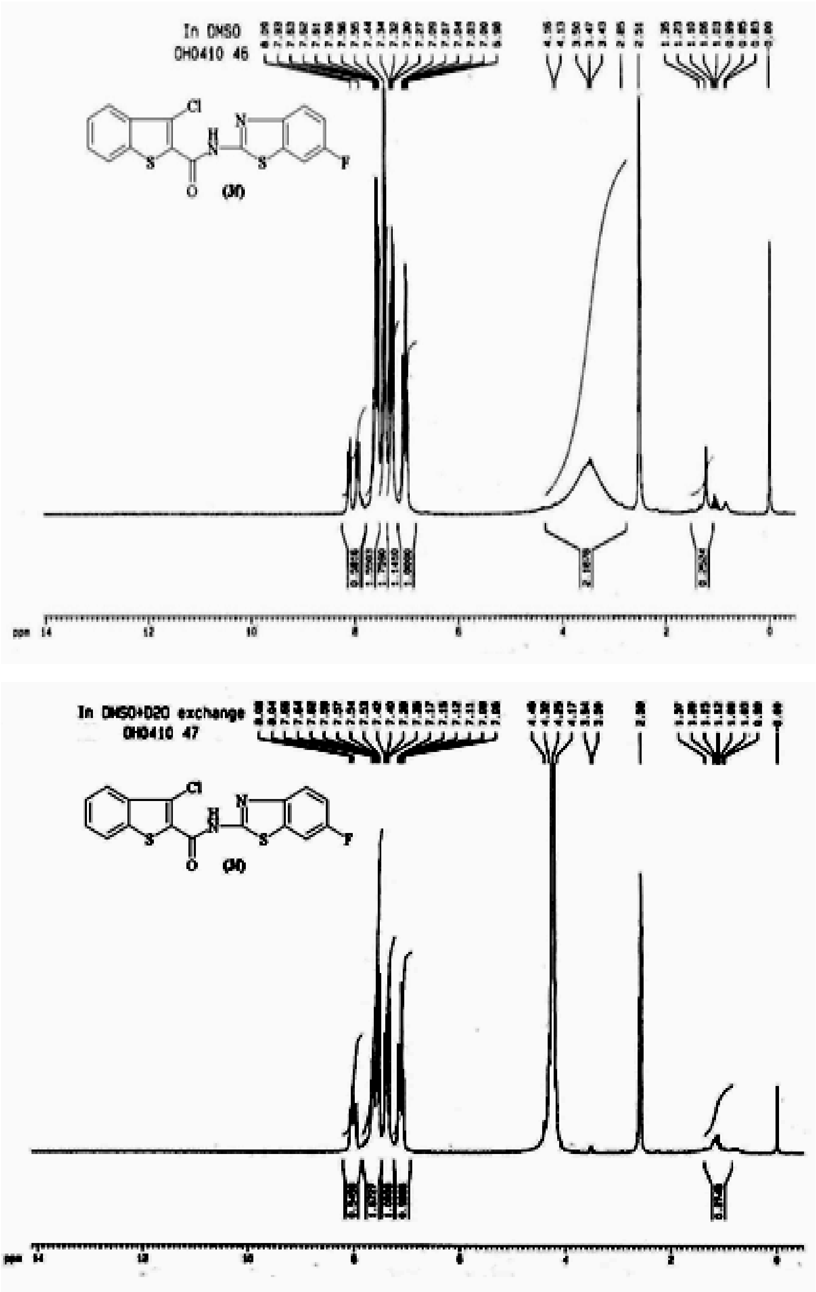


Figure No 5: ^{1}H NMR Spectra of Compound 3f.

^{1}H NMR (DMSO, δ ppm): 6.9 to 7.3 (3H, m, 3H of Ar-H), 7.4 to 7.5 (1H, s, 1H of CONH which was disappear in D_2O exchange), 7.5 to 7.9 (4H, m, 4H of Ar-H).

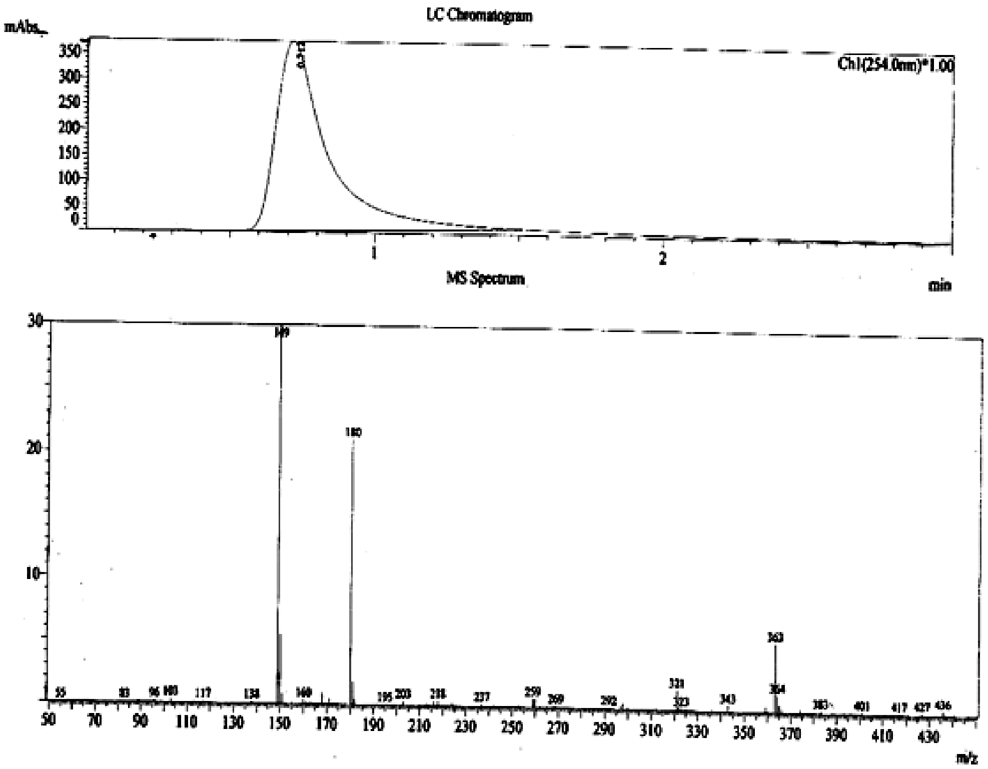


Figure No 6: Mass Spectra of Compound 3f.

LCMS (m/z): Molecular ion peak appear at 363 as (M+1).

Mol. Formula: $C_{16}H_8N_2OS_2ClF$.

Mol. Wt. : 362

Melting Point: 226 ^oC

Anthelmintic Activity

Indian adult earthworms were selected to study the antihelmintic activity. The earth- worms were collected from the water logged areas of soils in Kalaburagi, Karnataka, India. Earthworms were washed with normal saline to remove all the fecal matter and waste surrounding their body. The earth worms (*Pheritima posthuma*) 5-8 cm in length and 0.2-0.3 cm width weighing 0.8-3.04 g were used for experimental protocols. As the earthworms are resembled anatomically and physiologically with the intestinal roundworm parasites of human beings, hence they were selected to study the anthelmintic activity.

Table No 3: Anthelmintic activity of Benzothiophene compounds.

Sl.No	Compounds	Dose	Paralysis time (Minute)	Death time (Minute)
			Mean±S.E.M	Mean±S.E.M
1	3a	50mg/ml	24±0.48	31±0.60
2	3b	50mg/ml	25±0.44	33±0.36
3	3c	50mg/ml	31± 0.32	35±0.54
4	3d	50mg/ml	22±0.54	28±0.30
5	3e	50mg/ml	21±0.60	30±0.26
6	3f	50mg/ml	20±1.91	24±0.57
7	Control (Normal saline)	-------	-------	------
8	Albendazole	50mg/ml	21±1.52	22±4.50

Procedure

Gum acacia solution (1%) was prepared by using normal saline. Test solutions (50mg/ml) were prepared by using Gum acacia solution. Samples were taken in petriplates and adult healthy earth warms (n=6) were introduced into petriplates. Observations were made for the time taken to paralyze and time taken for death of the earthworms. Paralysis was said to occur when the worms do not revive even in normal saline. Death was concluded when worms lost their motility followed by fading away of the body color and the values are summarized in Table 3.

RESULT AND DISCUSSION

The prepared compounds along with their reaction time period and percentage yields were given in Table 2. It was found better yields (50-58%) with pure product as compared to the standard marketed miraculous drug. All the synthesized compounds were screened for anthelmintic activity. The data in the Table No 3 indicate that compound 3d, 3e and 3f were exhibited a broad spectrum anthelmintic activity. While other synthesized compounds of this series shown poor anthelmintic activity.

CONCLUSION

From the data of the anthelmintic activity it is clearly concluded that some of the synthesized compounds are promisingly significant. From the above results one can establish that the synthesized substituted benzothiophene can be rich source for the exploitation. Therefore in search of new generation of the active compounds modification of the benzothiophene nucleus have resulted in a large number of compounds having diverse pharmacological activities. The synthesis, structure and biological activities of benzothiophene derivatives have been long focused for research interest in the field of medicine, due to potential activities exhibited by them. Further the detail structure activity relationship studies are required along with the molecular manipulation i.e. molecular modeling may give better drugs and further toxicological study is needed. Molecules prepared for the biological testing do not always turn out as potential new molecules, but may be intended to serve as models for evaluation of the hypothesis.

ACKNOWLEDGEMENTS

The authors are thankful to my beloved Principal and HOD, Department of Pharmaceutical Chemistry, RMES's College of Pharmacy, Kalaburagi, for providing laboratory facilities to carry out the synthesis and pharmacological activity of the compounds. We also acknowledge my colleagues for their good co-operation in this regard.

REFERENCES

1. Komppa G. Untersuchungen in der thionaphthengruppe. J Prakt Chem., 1929; 122(1): 319- 31.
2. Heid JV, Levine R. The acylation of furan and thiophene with aliphatic anhydrides in the presence of boron trifluoride-etherate. J Org Chem., 1948; 13(3): 409-12.
3. Thionapthene, Technical Bulletin of Jafferson Chemical Company, Inc. J Am Chem Soc., 1950; 72(10): 4433-6.
4. Ife RJ, Brown TH, Blurton P, Keeling DJ, Leach CA, Meeson ML et al. Reversible inhibitors of the gastric (h+/k+)-atpase. 5. Substituted 2, 4-diaminoquinazolines and thienopyrimidines. J Med Chem., 1995; 38(14): 2763-73.
5. Kondracki MLB, Martin ML, Guyot M. A new β-carboline alkaloid isolated from the marine sponge *Hyrtios erecta*. Tetrahedron Lett., 1996; 37(20): 3457-60.
6. Press JB, Mcnally JJ. Thiophene systems 10. The synthesis and chemistry of some thienopyridinols. J Heterocycl Chem., 1988; 25(5): 1571-81.
7. Tseriotis G, Aspinall IH, Worthington PA. Zeneca Ltd. Fungicides. US Patent, Sep 26, 2000; 6,124,356.
8. Berglund RA. Eli Lilly and Co. Intermediate useful for the asymmetric synthesis of duloxetine. US Patent, Feb 13, 1996; 5,491,243.
9. Talley JJ, Penning TD, Collins PW, Rogier, Donald JJ, Malecha JW et al. G D Searl and Co. Substituted pyrazolyl benzenesulfonamides for the treatment of inflammation. US Patent, Oct 8, 1996; 5,563,165.

10. Abdulla RF. Eli Lilly and Co. Antiviral pyridazine hydrazones. US Patent, Jun 2, 1987; 4,670,437.
11. Thor KB. Eli Lilly and Co. Treatment of incontinence. US Patent, Apr 28, 1998; 5,744,474.
12. Boar RB, Cross AJ, Gray DA, Green RA. Astra Aktiebolag. 1-heteroazolyl-1-heterocyclyl alkane derivatives and their use and their use as neuroprotective agents. US Patent, Mar 4, 1997; 5,607,956.
13. Hildering R, Mudrak A. The Harshaw Chemical Co. Acid zinc electroplating. US Patent, Jun 1, 1976; 3,960,677.
14. Miyazaki M, Yokota S, Ito Y, Ohba N, Wada N, Tachikawa S et al. Kumiai Chemical Industry Co Ltd and Ihara Chemical Industry Co Ltd. Nicotinic acid derivatives and herbicides. US Patent, Mar 2, 1999; 5,877,120.
15. Bagli JF, Ferdinandi E. American Home Products Corp. Thiophene ethanolamines. US Patent, Aug 8, 1978; 4,105,663.
16. Sum PE, Joseph JP, Ziegler, Carl JB, Moran DB, Lin YI. American Cyanamid Co. Piperazine derivatives. US Patent, May 11, 1993; 5,210,193.
17. Jones RA, Civcir PU. Extended heterocyclic systems 2. The synthesis and characterisation of (2-furyl)pyridines, (2-thienyl)pyridines, and furan-pyridine and thiophene-pyridine oligomers. Tetrahedron, 1997; 53(34): 11529-40.
18. Freenman F, Lee MY, Lue H, Wang X, Rodriguez E. 1-Thia-cope rearrangements during the thionation of 2-endo-3-endo-bis (aroyl)bicyclo[2.2.1]hept-5-enes. J Org Chem., 1994; 59(13): 3695-8.
19. Wynberg H and Kooreman HJ. The mechanism of the hinsberg thiophene ring synthesis. J Am Chem Soc., 1965; 87(8): 1739-42.
20. Mclntosh JM, Khalil H. A new thiophene synthesis. Can J Chem., 1975; 53: 209.
21. Prim D, Kirsch G. Synthesis of new 3-methylthio-4,5,6,7-tetrahydro benzo[c] thiophene 4-ones. Synth Common, 1995; 25(16): 2449-55.
22. Reddy KV, Rajappa S. Heterocycles, 1994; 37: 347.
23. Kaye IA, Roberts MI. Dialkylaminoalkyl esters of 2-amino-6-carboxy benzothiazole. J Am Chem Soc., 1951; 73(10): 4762-4.
24. Bitler B, McElroy WD. The preparation and properties of crystalline firefly luciferin. Arch Biochem Biophys, 1957; 72(2): 358-68.
25. Campaigne E, Verth VJE. Reaction of diethyl oxalate with some ortho-substituted anilines. J Org Chem., 1958; 23(9): 1344-6.

26. Patil CB, Mahajan SK, Katti SA. Chalcone: A Versatile Molecule. *J Pharm Sci* and *Res.*, 2009; 1(3): 11-22.
27. Nidhi S, Ahmad S, Alam MS. Biological Potentials of Chalcone: A Review. *Int J of Pharm and Biolog Arch*, 2012; 3(6): 1298-303.
28. Trivedi AR, Dodiya DK, Ravat NR, Shah VH. Synthesis and biological evaluation of some new pyrimidines via novel chalcone series. *ARKIVOC*, 2008; 11(1): 131-41.
29. Kachroo M, Panda R, Yadav Y. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. *Der Pharma Chemica*, 2014; 6(2): 352-9.
30. Ahmed MA. Synthesis, characterization and antibacterial activity of (E) +Chalcone derivatives. *Eur. J. Chem*., 2013; 4(3): 207-10.
31. Jyothi MV, Prasad YR, Venkatesh P, Reddy MS. Synthesis and Antimicrobial Activity of Some Novel Chalcones of 3-acetyl Pyridine and their Pyrimidine Derivatives. *Chem. Sci. Trans.,* 2012; 1(3): 716-22.
32. Jin C, Liang Y, He H, Fu H. Synthesis and antitumor activity of novel chalcone derivatives. *Biomedicine and Pharma*., 2013; 67(3): 215-7.
33. Kachroo M, Panda R, Yadav Y. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. *Pharm. Chem.*, 2014; 6(2): 352-9.
34. Dudhe R, Sharma PK, Verma PK. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. *Int J Res Dev Pharm Life Sci*., 2015; 4: 1.