Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME SUBSTITUTED AZETIDINONE DERIVATIVES

Osman Ahmed*[1], Pankaj Sharma[2], Jaya Sharma[2]

[1]Research Scholar, Pacific University, Udaipur, Rajasthan.

[2]Department of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India.

***Received:* 10 Sept. 2013,** ***Revised and Accepted:* 25Sept. 2013**

ABSTRACT

The main obejcetive of this study is to synthesis 3-Chloro-4-substitutedphenyl-1-[{4-(-1-naphthyl)-1, 3-thiazol-2-yl} amino] azetidine-2-ones (A_1-A_{15}) from 1-acetyl naphthalene. The synthesized compound, characterized on the basis of satisfactory analytical and spectral (IR, H^1NMR, Mass) data, have shown moderate to good anticonvulsant activity.

KEYWORDS: *Anticonvulsant activity, 1-Acetylnaphthalene, Thiazoles, Azetidinones*

INTRODUCTION

Azetidinones, commonly known as β-lactams which are part of antibiotics structure are known to exhibit interesting biological activities. A good number of azetidinones possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant & antitubercular activities. They also function as enzyme inhibitors & are effective on the central nervous system [1]. The activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring [2].

*For Correspondance:
Mr. Osman Ahmed
Department of Pharmaceutical Chemistry,
Pacific University,
Udaipur, Rajasthan.
Email: ahmed.osman1602@gmail.com
Contact No- +919908177460

Such biological activities include antifungal, antitubercular, antitumor, cholesterol absorption inhibition and enzyme inhibition activity [3-17]. The β-lactams also serve as synthons for many biologically important classes for many biologically important classes of organic compounds [3]. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.

MATERIALS AND METHODS

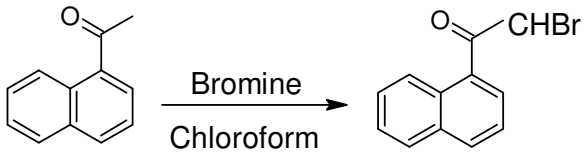
Chemicals and reagents:

1-acetylnaphthalene, chloroform, bromine, Substituted benzaldehyde thio semicarbazones, ethanol, thiolactic acid, dioxane, zinc chloride.

Method of Synthesis:

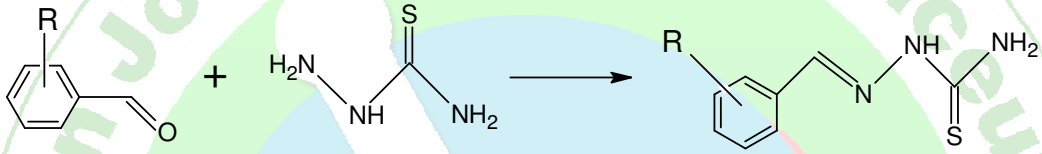
Synthesis of 1-bromoacetyl naphthalene:
1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to

flask containing 1-acetylnaphthalene solution, drop wise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding 1-bromoacetyl naphthalene.



Synthesis of substituted thiosemicarbazone:

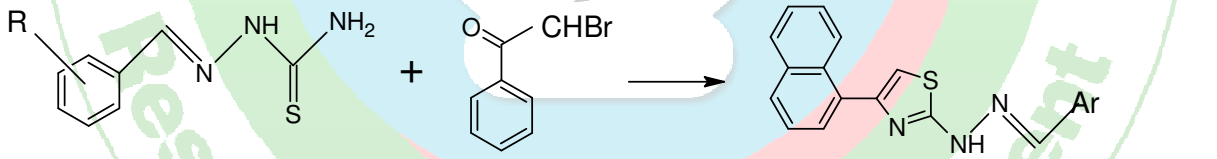
A solution of 0.05 mol. Substituted benzaldehyde in warm alcohol (300 ml) and a solution of 0.05 mol thiosemicarbazide in 300 ml water were mixed slowly. The product, which separated, was filtered off after cooling and recrystallised from ethanol. Other thiosemicarbazones were prepared in the same way.



Substituted Benzaldehyde Thiosemicarbazide Substituted benzaldehyde thiosemicarbazone

Synthesis of 4-naphthalen-1-yl-2-{2-[(substituted phenyl) methyl idene] hydrazino}-1, 3- thiazole:

Equimolar quantities (0.01 mole) of 1-bromoacetylnaphthalene and substituted benzaldehyde thiosemicarbazones were dissolved in 50 mL of ethanol in a 100 ml round bottom flask. The reaction mixture was refluxed for 1-2 h. A solid was separated during refluxing which was hot filtered, dried and recrystallized from ethanol yielding 4-naphthalen-1-yl-2-{2- [(substituted phenyl) methylidene] hydrazino}-1,3-thiazole.

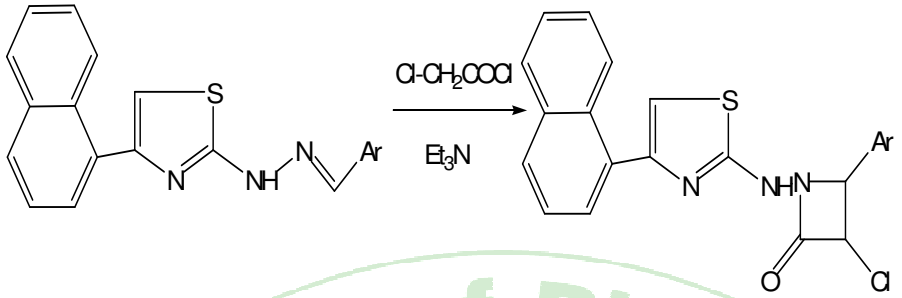


Substituted benzaldehyde thiosemicarbazone 1-Bromoacetyl napthalene 4-Naphthalene-1-yl-2-{[(substituted phenyl) methylidene] hydrazino}-1,3-thiazole

Synthesis of 3 – Chloro – 4 – Substituted phenyl - 1 - [{4 - (- 1 – Naphthyl)-1, 3-Thiazol-2-yl} Amino] Azetidin-2-ones (A1-A15)

A solution of chloroacetyl chloride (0.02 moles) in dry dioxane (30 ml) was added drop wise below 10 °C to a well stirred solution of 4-(1- naphthyl)-2-(substituted benzylidine amino)-1,3- thiazoles (A1-A15) (0.01 mole) and triethylamine (0.02 moles) in dimethylformamide (10 ml). The solution was stirred for 8-10 hr. The reaction mixture was filtered (to remove precipitates of triethylamine hydrochloride) and poured into ice cold water. The resulting solid was separated by vacuum filtration and dried. The compound was recrystallized from dioxane.

The purity of the compounds was established on the basis of TLC.



$(A_1 - A_{15})$

General Procedures:

Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. 1HNMR spectra were recorded on bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million(ppm). Splitting patterns are designated as follows: S-Singlet, d-doublet, t-triplet, q-quartet and m-multiplet. Mass spectra (MS) were recorded on Shimadzu GC-MS operating at 70eV .All the synthesized compounds were purified by recrystallization. The reaction were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultra violet light.

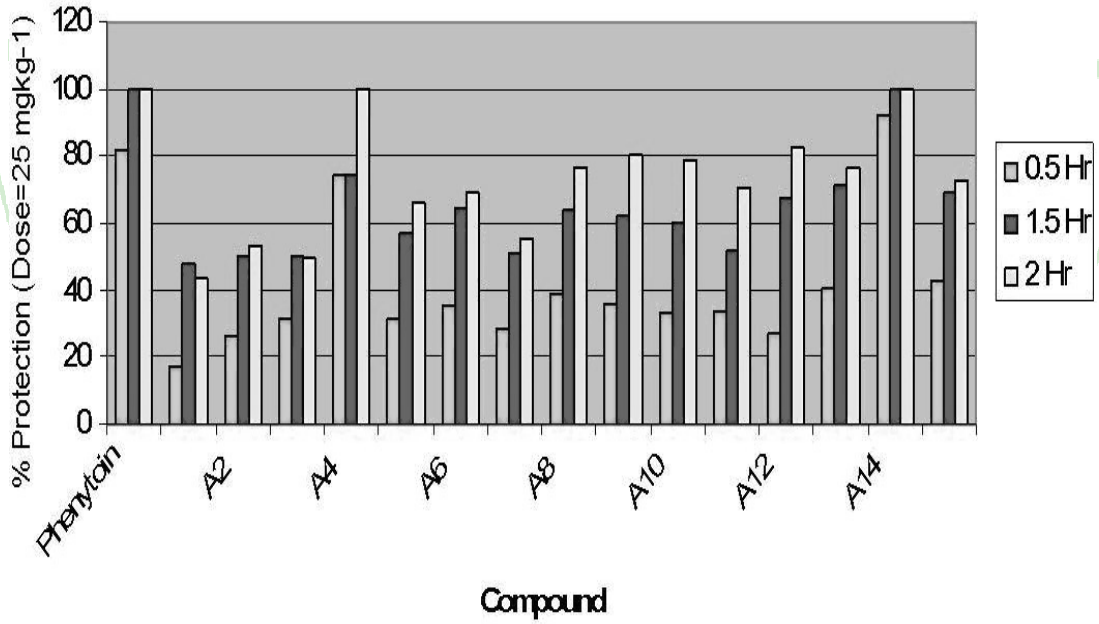


Figure I Anticonvulsant activity of 3-Chloro-4-substitutedphenyl-1-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino] azetidin-2-ones (A1-A15) by AEBT Model (Dose=4 mgkg-1)

PHARMACOLOGICAL STUDIES

Table No I Anticonvulsant activity of 3-Chloro-4-substitutedphenyl-1-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino] azetidin-2-ones (A1-A15) by AEBT Model (Dose=4 mgkg-1).

Compound	% Protection (Dose=25 mgkg-1)		
	0.5 Hr	1.5 Hr	2 Hr
Phenytoin	81.47 ± 1.22	100 ± 0.00	100.00 ± 0.00
A1	17.22 ± 0.428	47.95 ± 0.557	43.84 ± 0.494
A2	26.09 ± 0.477	50.00 ± 0.881	53.57 ± 0.341
A3	31.79 ± 0.210	50.00 ± 0.494	49.29 ± 0.477
A4	74.45 ± 1.60***	73.97 ± 1.327***	100.00 ± 0.00***
A5	31.79 ± 0.421	56.85 ± 0.577	65.70 ± 0.542*
A6	35.09 ± 0.577*	64.66 ± 0.703**	69.29 ± 0.557**
A7	28.48 ± 0.477	50.68 ± 0.408	55.71 ± 0.307**
A8	39.34 ± 0.833**	63.69 ± 0.632**	76.43 ± 1.116**
A9	35.96 ± 0.421**	62.33 ± 0.428**	80.00 ± 1.376**
A10	32.98 ± 0.307	60.07 ± 0.600*	78.57 ± 0.730***
A11	33.77 ± 0.730	52.05 ± 0.516	70.70 ± 0.600
A12	27.15 ± 0.365	67.81 ± 1.820	82.14 ± 0.957
A13	40.39 ± 0.730	71.51 ± 1.376	76.43 ± 1.145
A14	92.32 ± 0.8332***	100.00 ± 0.00***	100.00 ± 0.00***
A15	43.05 ± 0.666	69.18 ± 1.857	72.86 ± 1.600

* p<0.05, ** p<0.01, *** p<0.001

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the basis of their IR, 1H NMR and elemental analysis. The study was aimed at evaluating the anticonvulsant effect of compounds on mice.

Anticonvulsant activity

The anticonvulsant activity of 3-Chloro-4-substitutedphenyl-l-[{4-(1-naphthyl)-1, 3-thiazol-2-yl} amino] azetidin-2-ones **(A1-A15)** by MES method revealed that two compounds namely, **A4** (Ar = 3-chlorophenyl) and **A14** (Ar = 3, 4-dimethoxyphenyl) showed highly significant activity comparable with standard, phenytoin. Compound **A9** (Ar = 4-bromophenyl) and **A12** (Ar = 4-dimethylaminophenyl) also exhibited good activity. All other compounds displayed mild to moderate activity after 2 hr.

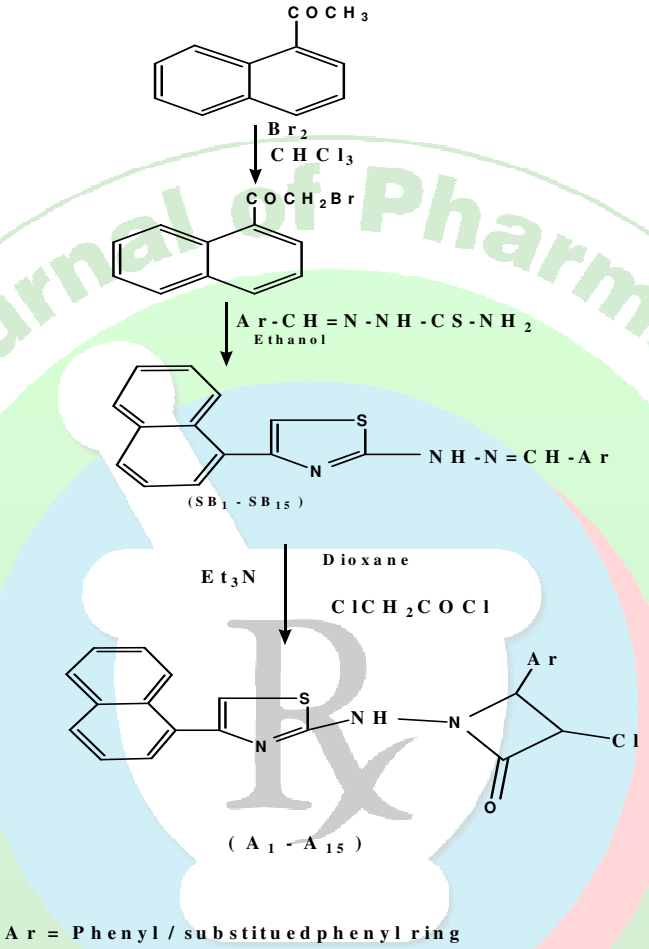
Structure Activity Relationship

- Compound having 3, 4-dimethoxyphenyl group showed significant and potent anticonvulsant activity than monomethoxy and trimethoxy derivatives.
- Nitro derivatives were found to possess moderate anticonvulsant activity.
- Compound **A4** (Ar = 3-chlorophenyl) exhibited potent anticonvulsant activity

while other mono and dichloro derivatives displayed moderate activity.

- Compound **A10** (Ar = 4-bromo-2-hydroxyphenyl) showed better activity than its chloro derivative.

Reaction Scheme



CONCLUSION

Above findings have resulted in the identification of compounds **(A3, A11, A15)** as new lead compounds for the development of anticonvulsant drugs.

REFERENCE

1. *Ameya A.Chavan and Nandini R.Pai., Synthesis and biological Activity of N-substituted-3-chloro-2-azetidinones, Molecules. 2007;12: 2467-2477.*
2. *Freddy H.Havaldar and Sushil Kumar J. Mishra., Synthesis of some azetidi-2-ones and thiazolidin-4-ones as potential antimicrobial Agents. Indian J.Heterocycl. Chem. 2004; 13: 197-200.*
3. *Patel K.H, Mehta A.G., Synthesis and antifungal activity of azetidinones and thiazolidinones derivative of 2-amino-6- (2-naphthalenyl) thiazole [3, 2-d] thiadiazole, E.J.Chem., 2006; 3 (13): 267-273.*
4. *Singh, G. S. Mini-Rev. Med. Chem. 2004; 4: 69.*
5. *Singh, G. S. Mini-Rev. Med. Chem. 2004; 4: 93.*
6. *Deshmukh, AR, Bhawal, BM, Krishnaswami, D., Govande, V.;Shinkre, B. A.; Jayanthi, A. Curr. Med. Chem. 2004, 11, 1889; Alcaide, B.;Almendros,P. Curr. Med. Chem. 2004; 11: 1921.*
7. *Staudinger, H. Liebigs. Ann. Chem. 1907; 356: 51.*
8. *Banik, B. K., Becker, F. F. Tetrahedron Lett. 2000; 41: 6551*
9. *Singh, G. S. Curr. Org. Synth. 2005; 2: 377.*
10. *Singh, G. S.; Mmolotsi, B. J. Il Farmaco 2005; 60: 727.*
11. *Singh, G. S.; Mmolotsi, B. J. J. Heteocycl. Chem., 2006.*
12. *Singh S, B.; Mehrotra, K. N. Can. J. Chem. 1982; 60: 1901.*

13. Singh, G. S.; Mehrotra, K. N. Ind. J. Chem. 1985; 24B: 129.
14. Singh, G. S.; Singh, T.; Lakhan, R. Nat. Acad. Science Lett. 1997; 20: 49.
15. Pheko, T.; Singh, G. S. Lett. Org. Chem. 2006; 3: 212.
16. Nenitzescu, C. D.; Solomonica, E. Org. Synth. Coll. 1950; 2: 496.
17. Hostettmann, K.; Marston, A.; Wolfender, J. L. Chimia 2005; 59: 291.
18. Rahalison, L.; Hamburger, M.; Hostettmann, K.; Monod, M.; Frenk, E. Phytoche.l Anals. 1991;2:199.
19. Saxena, G.; Farmer, S.; Towers, G. H. N.; Hancock, R. E. W. Phytochem. Anals. 1995; 6: 125.