ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

RESEARCH ARTICLE

An effective multicomponent synthesis of 2,6-dihydro-2,6-diimino-4,8-bis (phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile

Anil B. Chidrawar[1]*, Rajkumar U. Pokalwar[1], Nitishkumar S. Kaminwar[2]
[1]P G Research Centre, Department of Chemistry, Degloor College, Degloor,
S.R.T.M.U. Nanded, India – 431717
[2]P G Department of Chemistry, L. B. S. College, Dharmabad, S.R.T.M.U. Nanded, India - 431717
*Corresponding Author E-mail: **anilchidrawar74@gmail.com**

ABSTRACT:
A mixture of Bis methylthio methylene malononitrile (BMMM), thiourea and aniline/4-chloro aniline/4-methoxy aniline/4-nitro aniline on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, washed with water gives 2,6-dihydro-2,6-diimino-4,8-bis (phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile and its derivatives respectively. The synthesized compounds were characterized by elemental analysis and spectral data.

KEYWORDS: Bis methylthio methylene malononitrile, thiourea, 4-substituted anilines, K_2CO_3, dimethyl formamide.

INTRODUCTION:
Heterocyclic chemistry research encompasses almost half of the organic chemistry research throughout the world. A huge amount of bioactive organic compounds that contain heterocyclic frameworks play a vital part in the medicinal field. It is commonly reported that heterocycles having sulphur or nitrogen atoms or both of them are the general features present in the structures of most of the pharmaceutical and natural compounds.[1] They also act as multidentate ligands for different metals due to the presence of nitrogen and sulfur atoms and are thus used extensively in coordination chemistry to obtain new frameworks with potential bioactivity.[2]

A literature survey has revealed the diversified biological and pharmacological significance of several nitrogen and sulphur heterocycles. This aspect has been drawing the attention of many researchers towards exploiting the biological importance of various heterocyclic compounds and to establish the relationship between their biological, pharmacological potency and structural features.

Received on 27.08.2019 Modified on 14.10.2019
Accepted on 15.11.2019
Research J. Pharm. and Tech 2020; 13(6):2658-2660.
DOI: 10.5958/0974-360X.2020.00472.2

A rapid progress in the work on fused quinazolinones and thienopyrimidines has given rise to a number of compounds exhibiting potent pharmacological actions.

Heterocycles containing nitrogen and sulphur atoms, for instance thiazines, display diverse properties such as antifungal,[3] anti-HIV,[4] antipsoratic[5] and antimicrobial[6] activities and thus are of great chemical and pharmaceutical significance.[7-16] Some benzodiazepine substitutes[17] of imidazo [2,1-b]-[1,3] thiazines and pyrimido [2,1-b]-[1,3] thiazines are well known anti-inflammatory agents.[18] Likewise, thiazoles have also been reported to possess an important role in various fields of medicinal and agricultural chemistry.

There are a large number of pharmacologically interesting benzimidazole molecules fused to a five membered rings containing one heteroatom (pyrrolobenzimidazoles), two heteroatoms (pyrazolo-, imidazo-, oxazolo-, and thiazolo-benzimidazoles) and three heteroatoms (triazolo-, thiadiazolo- and oxadiazolo-benzimidazoles). Also, several benzimidazole moieties are fused to a six membered ring containing one heteroatom (pyridobenzimidazoles), two heteroatoms (pyrimido-, pyrazino-, thiazino-benzimidazoles) and three heteroatoms (triazinobenzimidazoles). Seven membered rings fused

to benzimidazole (azepino-, diazepino-, triazepino- and thiazepinobenzimidazoles) are also well known. It has been well focused that the presence of pyrimido-thiazine with various chemically reactive moieties is an important structural feature and also substituted imino group present in thiazine ring, and the resulting molecule would exhibit promising biological activities in continuation of our work.

In recent years, the synthesis of fused bicyclic heterocyclic compounds possessing pyrimido-oxazine and pyrimido-thiazine central core has been the focus of great interest. This type of compounds shows various biological properties such as antibacterial, antiallergic, anti-inflammatory, antitumor, phsphodiesterase inhibition and antiparkinsonism. thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities.

Experimental Section :

All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded with potassium bromide pellets technique, ^{1}H NMR spectra were recorded on AVANCE 300 MHz Spectrometer in DMSO using TMS as internal standard. Mass spectra were recorded on a FT VG-7070 H Mass Spectrometer using EI technique at 70 eV. All the reactions were monitored by Thin layer chromatography.

MATERIALS AND METHOD:

Experimental:

1) Synthesis of 2,6-dihydro-2,6-diimino-4,8-bis (phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IVa).

A mixture of Bis methylthio methylene malononitrile (BMMM) (2 moles), thiourea (1 mole) and aniline (2 moles) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis (phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 67 %, M.P. : 182 C. **IR:** (KBr/cm^{-1}): 3451 (=NH), 3105 (Ar-H), 2210 (-CN), 1622 (C=N); **^{1}H-NMR**: (DMSO): δ 4.02 (s 2H N-H), δ 6.46 (d 4H Ar-H), δ 6.62 (d 2H Ar-H), δ 7.01 (d 4H Ar-H), δ 8.55 (s 2H =NH); MS: (m/z : RA %): = 411 (M+1); **Elemental analysis**: $C_{21}H_{14}N_8S$, Calculated: (%) C 61.45, H 3.44, N 27.30, S 7.81 Found (%) : C 61.41, H 3.40, N 27.25, S 7.76

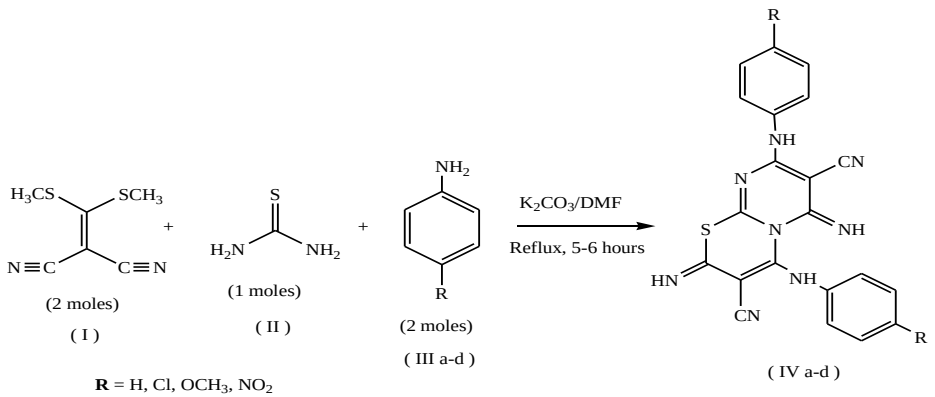
2) Synthesis of 4,8-bis(4-chlorophenylamino)-2,6-dihydro-2,6-diiminopyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IVb).

A mixture of Bis methylthio methylene malononitrile (BMMM) (2 moles), thiourea (1 mole) and 4-chloro aniline (2 moles) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis (4-chloro phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 63 %, M.P. : 177 C. **IR:** (KBr / cm^{-1}): 3450 (=NH), 3102 (Ar-H), 2210 (-CN), 1620 (C=N); **^{1}H-NMR**: (DMSO) : δ 4.01 (s 2H N-H), δ 6.40 (d 4H Ar-H), δ 7.02 (d 4H Ar-H), δ 8.51 (s 2H =NH); MS: (m/z : RA %): = 480 (M+1); **Elemental analysis** : $C_{21}H_{12}Cl_2N_8S$, Calculated: (%) C 52.62, H 2.52, Cl 14.79, N 23.38, S 6.69 Found (%) : C 52.60, H 2.50, Cl 14.75, N 23.34, S 6.66

3) Synthesis of 4,8-bis(4-methoxyphenylamino)-2,6-dihydro-2,6-diiminopyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IVc):

A mixture of Bis methylthio methylene malononitrile (BMMM) (2 moles), thiourea (1 mole) and 4-chloro aniline (2 moles) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis (4-methoxy phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.



R = H, Cl, OCH_3, NO_2

Yield : 56 %, M.P. : 167 ^{0}C. **IR:** (KBr / cm^{-1}): 3457 (=NH), 3107 (Ar-H), 2210 (-CN), 1621 (C=N); **^{1}H-NMR**: (DMSO) : δ 3.73 (s 6H CH_3), δ 4.00 (s 2H N-H), δ 6.35 (d 4H Ar-H), δ 6.52 (d 4H Ar-H), δ 8.50 (s 2H =NH); MS: (m/z : RA %): = 471 (M+1); **Elemental analysis**: $C_{23}H_{18}N_8O_2S$, Calculated: (%) C 58.71, H 3.86, N 23.82, O 6.80, S 6.81 Found (%) : C 58.70, H 3.82, N 23.80, O 6.75, S 6.77

4) Synthesis of 4,8-bis(4-nitrophenylamino)-2,6-dihydro-2,6-diiminopyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile (IVd):

A mixture of Bis methylthio methylene malononitrile (BMMM) (2 moles), thiourea (1 mole) and 4-chloro aniline (2 moles) on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours gives 2,6-dihydro-2,6-diimino-4,8-bis (4-nitro phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile. The product was filtered, washed with water and then dried. The product recrystallized from ethyl alcohol.

Yield : 71 %, M.P. : 161 C. **IR:** (KBr / cm^{-1}): 3451 (=NH), 3105 (Ar-H), 2209 (-CN), 1617 (C=N), 1340 & 1520 (-NO_2); **^{1}H-NMR :** (DMSO) : δ 4.05 (s 2H N-H), δ 6.72 (d 4H Ar-H), δ 7.94 (d 4H Ar-H), δ 8.51 (s 2H =NH); MS: (m/z : RA %): = 501 (M+1); **Elemental analysis**: $C_{21}H_{12}N_{10}O_4S$, Calculated: (%) C 50.40, H 2.42, N 27.99, O 12.79, S 6.41 Found (%) : C 50.37, H 2.40, N 27.95, O 12.75, S 6.37

RESULT AND DISCUSSION :

Bis methylthio methylene malononitrile (BMMM), thiourea and aniline/4-chloro aniline/4-methoxy aniline/4-nitro aniline on reflux with dimethyl formamide solvent in presence of K_2CO_3 for 5-6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, washed with water gives 2,6-dihydro-2,6-diimino-4,8-bis (phenylamino) pyrimido [2,1-b] [1,3] thiazine-3,7-dicarbonitrile and its derivatives respectively. The objectives of the present work are to synthesize certain pyrimido thiazine derivatives and study their biological properties. Thus an attempt has been made in this direction. As expected substituted pyrimido thiazine exhibited antibacterial, anti allergic, anti inflammatory, antitumor activities.

CONCLUSION:

In conclusion, we have synthesized simple and efficient novel fused bicyclic heterocycles pyrimido-oxazine having bis-electrophilic species reacting with various nucleophiles. The above informational data got from the literature gives an idea that thiazines are an important class of heterocyclic and their significances are challenging in disease of various infections. A survey of thiazine revealed that the moiety have possess a great deal of interest to the medicinal chemist and biochemist and can be taken as a lead molecule for designing potential bioactive compounds and thiazine derivatives have various pharmacological activities This review gives an idea to the researchers in determining the best and most productive, economical suggestive and clinically important compounds of thiazines. I hope that my brief review will help all those are interested to research in this class of heterocyclic compounds to develop potent pharmacologically active drugs in the field of medicinal chemistry. 1,3-thiazines are versatile molecules which require further research regarding synthesis and elucidation of mechanism of action of different derivatives by conducting invivo & invitro studies and QSAR development studies to bring the potential effects.

ACKNOWLEDGEMENTS :

The authors are grateful to Dr. Mohan Khatal, Principal, Degloor College, Degloor for providing laboratory facilities and IICT Hyderabad, for providing spectral data. The authors are also thankful to the Dr. S.V. Kuberkar, Ex. HOD, Dept. of Chemistry, Yeshwant Mahavidyalaya, Nanded for guided and valuable suggestions for this research work.

REFERENCES :

1. Deepika G., Gopinath P., Kranthi, G., Nagamani C., Jayasree Y.V., Naidu N.V., Enaganti S., J. Pharm. Res., 2012; 5: 1105–1107.
2. Chaviara A.T., Cox P.J., Repana K.H., Papi R.M., Papazisis K.T., Zambouli D., Kortsaris A.H., Kyriakidis D.A., Bolos C.A., J. Inorg. Biochem., 2004; 98: 1271–1283.
3. D.B. Reddy, S. Reddy, N.S. Reddy and M.V.R. Reddy, Indian J. Chem., Sect. B., 1991; 30: 529–533.
4. M.E. Arranz, J.A. Diaz, S.T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clercq and S. Vega, Bioorg. Med. Chem., 1999; 7: 2811–2822.
5. H. Moriyama, T. Tsukida, Y. Inoue, K. Yokota, K. Yoshino, H. Kondo, N. Miura and S. Nishimura, J. Med. Chem., 2004; 47: 1930–1938.
6. D. Armenise, G. Trapani, V. Arrivo and F. Morlacchi, Arch. Pharm., 1998; 331: 54–58.
7. G. Trippe, J. Perron, A.J. Marchand, V. Dupont, A. Guingant, J.P. Pradere and L. Toupet, Tetrahedron Lett., 2002; 43: 6067–6069.
8. M. Koketsu, K. Tanaka, Y. Takenaka, C.D. Kwong and H. Ishihara, Eur. J. Pharm. Sci., 2002; 15: 307–310.
9. M. Harmata, X. Hong and C.L. Barnes, Tetrahedron Lett., 2003; 44: 7261–7264.
10. T. Noshio, Y. Konno, M. Ori and M. Sakamoto, Eur. J. Org. Chem., 2001; 3533–3537.
11. L.D.S. Yadav and A. Singh, Tetrahedron Lett., 2003; 44: 5637–5640.
12. L.D.S. Yadav and S. Sharma, Synthesis, 1992; 919–920.
13. P. Pajesi, A. Foldesi, G. Batta and J. Tamas, Chem. Ber., 1989; 122: 651–653.
14. R. Okazaki, M. Unno and N. Inamoto,Heterocycles, 1987; 25: 183–190.
15. W. Hanfeld, Arch. Pharm., 1984; 317: 297–299.
16. K. Burger, E. Huber, W. Schontag and R. Ottlinger, J. Chem. Soc., Chem. Commun., 1983; 944–945.
17. (a) K. Kiec-Kononowicz, J. Karolak-Wojciechowska, C.E. Muller, B. Schumacher, E. Pekala and E. Szymanska, Eur. J. Med. Chem., 2001; 36: 407–419; (b) U. Geis, K. Kiec-Kononowicz and C.E. Muller, Sci. Pharm., 1996; 64: 383–390.
18. D. Bozsing, P. Sohar, G. Gigler and G. Kovacs, Eur. J. Med. Chem., 1996; 31: 663–668.