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Der Pharma Chemica, 2015, 7(11):205-209
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antioxidant, antimicrobial activity of 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3, 2-*a*] pyrimidines

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ABSTRACT

*New heterocyclic compound 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3, 2-a] pyrimidines **(3)** reported by reacting of 2-amino-5-methyl thiazole **(1)** with bis(methylthio) methylene malanonitrile **(2)**. Further the compound **(3)** was treated with aryl amines, substituted phenols, active methylene compounds and heteryl amines to obtain its 7-substituted derivatives. Newly synthesized thiazolo [3, 2-a] pyrimidines derivatives were screened for their antimicrobial and antioxidant activity.*

Keywords: Thiazolo [3,2-*a*] pyrimidines, anhydrous K_2CO_3, bis (methylthio)methylene malanonitrile, antimicrobial and antioxidant activity.

INTRODUCTION:

The literature survey reveals that thiazolo [3,2-*a*] pyrimidines shows prominent biological activities like antimicrobial[1-3], antibacterial[4], anti-inflammatory[5,6], antituberculosis[7], psychopharmological[8], antihypertensive[9]. In addition to this these thiazolo pyrimidines also function as calcium antagonist[10] diacetylglycerol (DG) kinase inhibitor[11], HIV-I reverse transcriptase inhibitor[12], group-2-metabolic glutamate receptor antagonists[13]. For the treatment of alzeimers disease, some thiazolo pyrimidines have been reported as new acetylcholesterase (ACHE) inhibitors[14]. Recently our research group synthesized some thiazolopyrimidines as potent antioxidant[15].

All these wide range of biological activities of different thiazolo [3,2-*a*] pyrimidines encourage us to synthesis some new thiazolo [3,2-*a*] pyrimidines. So, in this present investigation we report the synthesis of 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3,2- *a*] pyrimidines **(3)** and its 7-sustituted derivatives **(4a-e), (5a-e), (6a-d)** and **(7a-d)**.

MATERIALS AND METHODS

Open capillary tubes was used for melting points of newly synthesized compounds and were incorrected.. FTIR spectrometer was used for the IR spectra of compounds. were recorded on brucker advance 300 MHz spectrometer was used for ^{1}H-NMR spectra.. FT-VG-7070 Hz mass spectrometer has been utilized for Mass spectra ,using ESI technique.

General procedure:

Synthesis of 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3, 2- *a*] pyrimidine (3):

A equimolar mixture of 0.01mol of 2-amino-5-methylthiazole (1) and 0.01 mol of (2) was dissolved in DMF in presence of 10 mg of anhydrous K_2CO_3 was reflux for 3 hours. Containt of the reaction was left for cooling at room temperature then it stirred, pouring into crushed ice. The solid product get separated which was then filtered and recrystallized by using acetone-ethanol mixture to get pure **(3)**.

Synthesis of 7-substituted derivatives of 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3,2- *a*] pyrimidine (4a-7d):

A mixture of 0.01mol of compound (3) and independently with 0.01 mol of aryl amines, aryl phenols, active methylene compounds and heteryl amines in 15 ml DMF and 10 mg anhydrous K_2CO_3 was reflux for 3-4 hours. Containt of the reaction was left for cooling at room temperature then it stirred, pouring into crushed ice. The solid product get separated which was then filtered and recrystallized by using acetone-ethanol mixture to give pure compounds (4a-7d) respectively.

Spectra analysis:

6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo [3,2- *a*] pyrimidine (3):

Brown powder, Yield 80 %, M.P.196 °C (dec.). IR (KBr / cm-1) 3309 (=NH), 2204 (CN); ^{1}H NMR (300MHz, DMSO-d_6) δ 2.41 (s, 3H, -CH_3), 2.53 (s, 3H, -SCH_3), 7.25 (s, 1H), 7.98 (br, s, 1H). EI-MS (m/z: RA %): 237 M^{+1} 100%). ^{13}C NMR (300 MHz, DMSO–d6) δ: 14.6, 17.9, 63.1, 70.9, 120.8, 125,130.6,161.8, 172.9.

6-Cyano-5-imino-2-methyl-7-(4-methyl anilino)-5H-thiazolo [3,2-*a*]pyrimidine (4b):

Faint Brown powder, Yield 75 %, M.P.214 °C (dec.). IR (KBr / cm-1) 3299 (=NH), 2198 (CN); ^{1}H NMR (300MHz, DMSO-d_6) δ: 2.41 (s, 3H, -CH_3) 2.52 (s, 3H, -CH_3), 4.2 (s, 1H), 6.16-6.53 (m, 5H). EI-MS (m/z) 296 M^{+1}).

6-Cyano-5-imino-2-methyl-7-(4-nitro phenoxy)-5H-thiazolo[3,2-*a*]pyrimidine (5e):

Brown powder , Yield 87 %, M.P.217 °C (dec.). IR (KBr / cm^{-1}) 3301 (=NH), 2198.7 (CN); ^{1}H NMR (300MHz, DMSO-d_6) δ: 2.53 (s, 3H, -CH_3), 7.49-8.32 (m, 5H) 8.56 (s, 1H). EI-MS (m/z): 328 M^{+1}).

6-Cyano-5-imino-2-methyl-7-malonyl-5H-thiazolo [3,2- *a*]pyrimidine (6d):

Brown powder, Yield 76 %, M.P.232 °C (dec.). IR (KBr / cm^{-1}) 3299 (=NH), 2196.7 (CN); ^{1}H NMR (300MHz, DMSO-d_6) δ: 2.78 (s, 3H, -CH_3), 4.1 (s, 1H), 7.29 (s, 1H), 7.41 (s, 1H), EI-MS (m/z): 255 M^{+1}).

6-Cyano-5-imino-2-methyl-7-marpholino-5H-thiazolo [3,2- *a*]pyrimidine (7c):

Greenish grey powder, Yield 74 %, M.P.205 °C (dec.). IR (KBr / cm^{-1}) 3310 (=NH), 2200(CN); ^{1}H NMR (300MHz, DMSO-d_6) δ: 2.41 (s, 3H,), 3.83-3.84 (2H), 4.35-4.37 (2H), 7.95 (s, 1H), 8.47 (s, 1H), EI-MS (m/z): 276 M^{+1}).

Biological Activity:

1. Antimicrobial activity:

Using Kirbey –Bauer method for disc diffusion assay, selected compounds are tested for their antimicrobial activity. Antimicrobial activity of tested compounds are shown in the table .

Table: antimicrobial activitivy of tested compounds

Sr. No.	Compound	Zone of inhibition in mm	
		E. coli	***B. subtilis***
1	3	NR	NR
2	4a	14 ± 0.14	04 ± 0.82
3	4b	12 ± 0.58	03 ± 0.61
4	4c	12 ± 0.47	16 ± 0.59
5	5b	10 ± 0.89	26 ± 0.64
6	5e	12 ± 0.28	24 ± 0.73
7	6a	06 ± 0.76	10 ± 0.27
8	6b	16 ± 0.64	14 ± 0.67
9	6d	04 ± 0.47	16 ± 0.34
10	7c	18± 0.19	22 ± 0.46
11	Penicillin (Standard)	26 ± 0.39	28 ± 0.49

2. Antioxidant activity:
DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay:
Roberta R.[16] reported method has been followed for the DPPH radical scavenging assay .

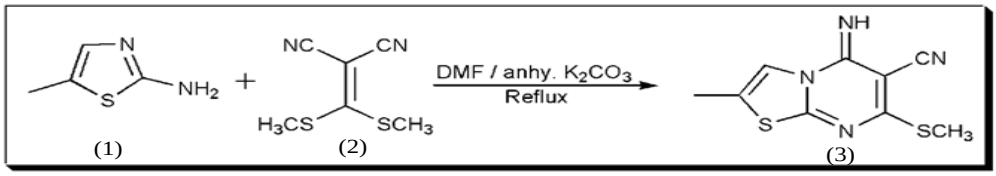
Some of the newly synthesized compounds has been screened for their antimicrobial activitivy and their results are shown in the following table.

Table: antioxidant activitivy of tested compounds.

Sr. No.	Compound	Antioxidant Activity
		DPPH radical scavenging activity (%)
1	3	40 ± 0.22
2	4a	41± 0.23
3	4b	54 ± 0.80
4	4c	59 ± 0.47
5	5b	63 ± 0.69
6	5e	81 ± 0.28
7	6a	65 ± 0.91
8	6b	76 ± 0.49
9	6d	52 ± 0.39
10	7c	73 ± 0.64
11	Penicillin (Standard)	86 ± 0.88

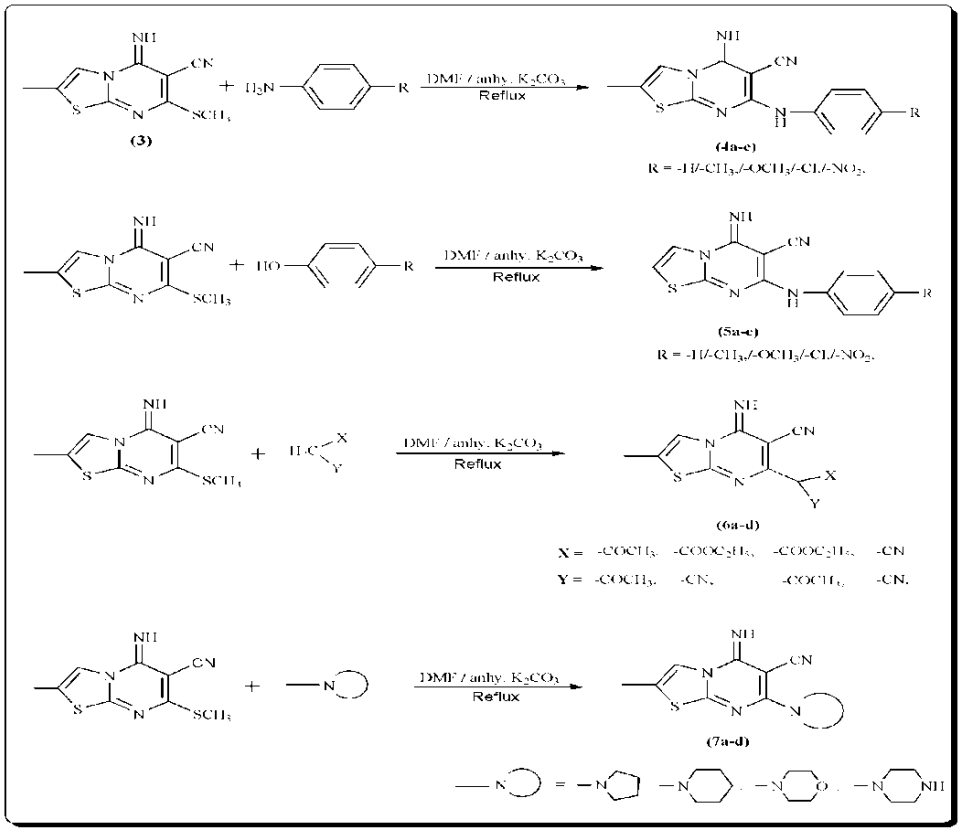
RESULTS AND DISCUSSION:

The parent molecule **(3)** was synthesized by the treatment of 2-amino-5-methyl thiazole **(1)** with bis(methylthio) methylene malanonitrile **(2)** in presence of DMF and anhydrous K_2CO_3 **(scheme-I)**.Analytical and specral data was used for structural recognition of newly reported compounds.



(1) (2) (3)

Scheme-I



Scheme – II

Active thiomethyl group is present in the parent compound **(3)** at 7-position.withdrawing nature of cyano group and nitrogen present in the ring activates the thiomethyl group. Due to the presence of active thiomethyl group in (3) susceptibility of this parent compound **(3)** for substitution with different selected nucleophiles such as aryl amines , substituted phenols , active methylene compounds and heteryl amines has been investigated. Hence, the molecule **(3)** separately reacted with aryl amines,substitutedphenols, compounds containing active methylene group , and some heterocyclic amine heteryl amines in DMF and anhydrous K_2CO_3 to afford new thiazolo pyrimidine compounds **4a-e, 5a-e, 6a-d, 7a-d** respectively **(scheme – II)**.

CONCLUSION

Simple and efficient synthesis of 6-cyano-5-imino-2-methyl-7(methylthio)-5H-thiazolo[3, 2-*a*]pyrimidines (3) and its 7-substituted derivatives (4a-7d) has been presented. Among these synthesized compounds (5e), (6b) showed remarkable antioxidant activity and compound (5b), (5e) and (7c) exhibit promising antimicrobial activity against B. substilis

The result of the present work demonstrate that thiazolo [3, 2-*a*] pyrimidines are potent antioxidant and antimicrobial agents and it will attract researchers to design new potent pharmacological thiazolo [3, 2-*a*]pyrimidines.

REFERENCES

[1] A Nagraj. and S.C. Reddy., *J. Iran Chem. Soc*, **2008**, 5(2), 262-267.
[2] D.B Anupkumar., G.K Prakash.., and K.M. Mahadevan, *Indian J. chem*, **2006**, 45B 1699-1703.
[3] H.H. Sayed., A.H. Shamroukh., A.E. Rashad., *Acta Pharm*, **2006**, 56, 231.
[4] R.A. Caburn, R.A. Glennon, *J. Pharm. Sci*. **1973**, 62, 1785.
[5] K.S. Nimawat, K.H. Popat, S.L. Vasovya and Joshi H.S., *Indian J. Heterocyclic Chem*., **2003**, 12, 217-220.

[6] A. O. S.A. Khan, N. A. Siddiqui W., *Med. Chem Res*. **2009**, 9267.
[7] B.J. Tozkoparan, M.J. Ertan, B.J. Kres, M. Lage, *Arch. Pharm. Med. Chem*., **1998**, 331, 201.
[8] Van Laar, Volkerts E. Verbaten M., *Psychopharmcology*, 2001, 154, 189.
[9] J. Nicolle, E. Benoit-Guyod M. Namil, A. J. Lederc A., *Eur. J. Med. Chem*. **1992**, 27, 115.
[10] B. A. Uma S. E. M. Wiegree, *Pharmazie*, **1992**, 47, 687.
[11] N. K. M. M. Nobe H. Sakai Y. T. J., Mornose K. B. *J. Pharmacol*, **2004**, 143, 166.
[12] J. R. Prondfort, *Expert opin. Ther. Pat*. **1998**, 8, 971.
[13] W. J. Kolezewski S.J. A. G. M. V. Woltering T., Bioorg. *Med. Chem. Lett*, **1999**, 9, 1573.
[14] H. Zhi, L. Chen, L. Zhang, S. Liu, D.C. Wan, C. Hu, Arkivoc**, 2008**, Xii, 266.
[15] S. P. Vartale, D. B. Kadam, N. K. Halikar and M. M. Pund Int. J. of *Drug Development & Research*, **2013**, 5 (1), 128-134.
[16] R. Roberta, C.C. Luciana, G.M. Luciana,. and P. Glaucia, *Journal of Food Sciences*, **2006**,71, 102-107.