Synthesis of 7-(4-Bromophenyl)-4, 7-Dihydro-5-Methyl-N-Phenyl Tetrazolo [1,5-A] Pyrimidine-6-Carboxamide

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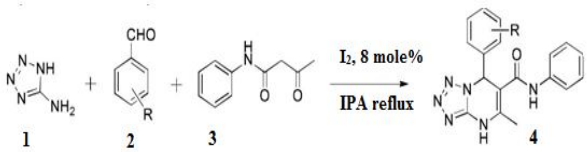
Abstract- *Pyrimidine nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities. A mixture of three-component condensation of 5-aminotetrazole **1**(0.01 mol), aromatic aldehyde **2**(0.01 mol),3-oxo-N-phenylbutanamide **3**(0.01mol) and (8 mol% I_2/i-PrOH) was dissolved in 10 ml isopropyl alcohol. The reaction mixture was refluxed for 3-4 hrs and then was cooled at room temperature. The resulting precipitate was filtered, washed with chilled isopropyl alcohol afforded the pure desired products **4**(PB-1-PB-10), (Scheme-1). The aim of our work is the synthesis of substituted tetrazolo[1,5-a]pyrimidine carboxamides. Some new tetrazolopyrimidine derivatives have been synthesized and characterization of these synthesized compounds is done by IR, NMR and mass spectral data*

Keywords- 5-aminotetrazole, tetrahydrotetrazolo[1,5-*a*]pyrimidine-carboxamide, i-PrOH.



Scheme-1

I. INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceeding complex and involves talent of people from variety of disciplines [1]. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity [2]. Pyrimidine is a six membered cyclic compound containing four carbon and two nitrogen atoms and is pharmacologically inactive but its synthetic derivatives possess an important role in modern medicine.

In medicinal chemistry, pyrimidine derivatives have been very well known for their therapeutic applications. The presence of a pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of possible reasons for their activities[3].In recent years, synthesis of Tetreazolopyrimidine and their derivatives is of high interest in organic chemistry[4-8].

Tetrazolopyrimidines are known to be synthesized using mineral acid[9], sulfamic acid[10], strontium chloride hexahydrate[11] etc. Recently, in synthetic organic chemistry, one-pot multi component reactions are very popular because of their significant advantages[12]. Chemo selective reduction of fused tetrazoles using phase-Transfer condition has been reported by Desai et al.[13-16].

Their related fused heterocycles are of interest as potential bioactive molecules. They are known to exhibit biological activities such as anti microbial[17], anti malerial[18], anti hypertensive[19], anti cancer[20], anti tumor[21], anti inflamatory[22], anti bacterial[23], analgesic, anti fungal[24] and anti viral[25] etc.

II. EXPERIENTIAL SECTION

Materials and Method

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The formation of the compounds was checked by thin-layer chromatography and accomplished on 0.2-mm pre coated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor.

The characterization of all these compounds was done by IR, NMR and mass spectral data. The IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. The Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR was determined in DMSO solution on a Bruker Ac 400 MHz spectrometer.

Synthesis of 7-(4-bromophenyl)-4, 7-dihydro-5-methyl-N-phenyl tetrazolo [1,5-a] pyrimidine-6-carboxamide (PB-1-PB-10):

A mixture of 3-oxo-N-phenylbutanamide (0.01mol), aromatic aldehyde (0.01 mol), 5-aminotetrazole (0.01 mol) and (8mol% I_2/i-PrOH) was dissolved in 10 ml isopropyl alcohol. The reaction mixture was refluxed for 3-4 hrs and then was cooled at room temperature. The resulting precipitate was filtered, washed with chilled isopropyl alcohol to give pure product. The yield percentage and M.F of all the synthesized compounds are given in Table-1.

Table-1: yield percentage and M.F of tetrazolopyrimidine derivatives.

Entry	R	M.F	Yield (%)
PB-1	4-OH	$C_{18}H_{16}N_6O_2$	68
PB-2	2,5diOCH$_3$	$C_{20}H_{20}N_6O_3$	69
PB-3	4-Br	$C_{18}H_{15}BrN_6O$	74
PB-4	4-CH$_3$	$C_{19}H_{18}N_6O$	68
PB-5	2-OCH$_3$	$C_{19}H_{18}N_6O_2$	79
PB-6	4-NO$_2$	$C_{18}H_{15}N_7O_3$	75
PB-7	3-Cl	$C_{18}H_{15}ClN_6O$	76
PB-8	3-NO$_2$	$C_{18}H_{15}N_7O_3$	78
PB-9	3-OCH$_3$	$C_{19}H_{18}N_6O_3$	80
PB-10	3-Br	$C_{18}H_{15}BrN_6O$	72

Spectral data

7-(4-hydroxyphenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5a]pyrimidine-6-carboxamide (PB-1): m.p. 140-142°C; IR (KBr): 3626(O-H), 3455(N-H), 3304(N-H), 3034(Ar, C-H), 2943(C-H), 1683 (C=O), 1540(Ar,C=C), 1520(C-N), 1495(Ar,C=C), 1478(C-H), 1053(C-O) cm^{-1}; MS: *m/z* = 348 [M]$^+$

7-(2,5-dimethoxyphenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-2): m.p.128-130°C; IR (KBr): 3452(N-H), 3304(N-H), 3034(Ar, C-H), 2942(C-H), 1682 (C=O), 1542(Ar,C=C), 1520(C-N), 1496(Ar,C=C), 1478(C-H), 1152(C-O-C)cm^{-1}; MS: *m/z* = 392 [M]$^+$

7-(4-bromophenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-3): m.p. 162-164°C; IR (KBr): 3483(N-H), 3377(N-H), 3198 (Ar, C-H), 2943(C-H), 1672 (C=O), 1530(Ar, C=C), 1589(C-N), 1489(Ar,C=C), 1450(C-H), 1068(C-O),756(C-Br) cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.51 (s, 3H, -CH$_3$), 5.32 (s, 1H, -CH), 6.90-6.94 (t, 3H,- ArH), 7.33-7.35 (d, 2H, ArH), 7.47-7.49 (d, 2H, ArH) 7.87-7.89 (d, 2H, ArH), 9.94 (S, 1H, -NH), 10.73 (S, 1H, -NH), 13C NMR (100 MHz, DMSO): δ ppm 17.38, 55.39, 104.84, 112.62, 113.93, 114.70, 115.85, 122.91, 127.84, 137.00, 147.77, 153.82, 160.08. MS: *m/z* =411 [M]$^+$

5-methyl-N-phenyl-7-(p-tolyl)-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide(PB-4): m.p. 154-156°C; IR (KBr): 3452(N-H), 3350(N-H), 3031(Ar, C-H), 2944(C-H), 1682 (C=O), 1520(C-N), 1497(Ar,C=C), 1454(C-H)cm^{-1}; MS: *m/z* = 346 [M]$^+$

7-(2-methoxyphenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5a]pyrimidine-6-carboxamide (PB-5): m.p. 134-136°C; IR (KBr): 3456(Amide, N-H), 3343(N-H), 3023(Ar, C-H), 2946(C-H), 1687 (C=O), 1543(Ar,C=C), 1492(Ar,C=C), 1454(C-H), 1153(C-O-C) cm^{-1}; MS *m/z* = 362 [M]$^+$

5-methyl-7-(4-nitrophenyl)-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-6): m.p. 150-152°C; IR (KBr): 3432(N-H), 3336(N-H), 3053(Ar, C-H), 2954(C-H), 2830(C-H), 1678 (C=O), 1531(Ar,C=C), 1525(C-N), 1486(Ar,C=C), 1473(C-H)cm^{-1}; MS: *m/z* =377 [M]$^+$

7-(3-chlorophenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-7): m.p. 144-146°C; IR (KBr): 3452(N-H), 3334(N-H), 3037(Ar, C-H), 2946(C-H), 1689 (C=O), 1540(Ar,C=C),1520(C-N),1495(Ar, C=C), 1474(C-H), 755(C-Cl)cm^{-1}; MS: *m/z* = 366 [M]$^+$

5-methyl-7-(3-nitrophenyl)-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-8): m.p.159-161°C; IR (KBr): 3438(N-H), 3354(N-H), 2954(Ar, C-H), 2830(C-H), 1684 (C=O), 1517(Ar,C=C),1486(Ar,C=C),1472(C-H)cm^{-1}; MS: *m/z* = 377 [M]$^+$

7-(4-hydroxy-3-methoxyphenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-9): m.p.167-169°C; IR (KBr): 3638(O-H), 3443(Amide, N-H), 3310(N-H), 3034(Ar, C-H), 2944(C-H),1686 (C=O),1530(Ar, C=C), 1497(Ar, C=C), 1459(C-H),1160(C-O-C) 1053(C-O)cm^{-1}; MS: *m/z* = 378 [M]$^+$

7-(3-bromophenyl)-5-methyl-N-phenyl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxamide (PB-10):m.p.172-174°C; IR (KBr): 3446(N-H), 3354(N-H), 3022(Ar, C-H), 2941(C-H), 1689 (C=O), 1530(Ar, C=C), 1481(Ar, C=C), 1471(C-H), 722(C-Br) cm^{-1}; MS: *m/z* = 411 [M]$^+$

REFERENCES

[1] S. M. Desenko, and V. D. Orlov1.*Chemistry of Heterocyclic Compounds.,* 2001, *37,6.*

[2] V. L. Gein and M. V. Dmitriev, *Russian Journal of Organic Chemistry., **2016**,52, 4,558–561.*

[3] Fedorova, O. V.; Rusinov, G. L. and Ovchinnikova, I. G.; *Russ. Chem. Bull. Int. Ed.* **2003,** 52, 1768-1769.

[4] Celewicz, L. and Golankiewicz, K.; *Biochem. Biophy. Res. Comm.***1992,** 187(3), 1545-1550.

[5] Roschger, P. and Färber, G.; *J. Heterocyc. Chem.* **1993,** *30(5),* 1267-1271.

[6] Desai, N. D. *Synth. Comm.* **2006,** *36(15),* 2169-2182.

[7] Abu-Zied, K. M. and Hassan, N.; A.; *J. Chin. Chem. Soc.* **2008,** *55,* 209-216.

[8] Gein, V. L.; Mishunin, V. V.; Tsyplyakova, E. P.; Vakhrin, M. I. and Slepukhin. P. A.; *Russ. J. Org. Chem.* **2011,** *47(7),* 1077-1082.

[9] F Rusinov and Ovchinnikova, I. G.; *Russian Chem. Bull. Int. Ed*. **2003,** 52, 1768-1769.

[10] Wang, C.; Yu, C. and Tu, S.; *J. Heterocy. Chem.* **2008,** *45,* 1609-1613.

[11] Chitra S. and Pandiarajan K. *Eur. J. Med. Chem.* **2010,** *45,* 367–371.

[12] Zeng L.-Y. and Cai C.; *J. Comb. Chem.* **2010,** *12,* 35–40.

[13] Desai, N. D. and Shah, R. D.; *Synthesis* **2006,** *19,* 3275-3279.

[14] Herr, R. J.; *Bioorg. Med. Chem.* **2002,** *10,* 3379-3393.

[15] Bondock, S. and Metwally, M. A.; *Eur. J. Med. Chem.* **2009,** *44,* 4813 –4818.

[16] Devanathan, D. and Pandiarajan, K.; *Eur. J. Med. Chem.* **2010,** *45,* 367–371.

[17] Biot, C. and Davioud-Charvet, E.; *J. Med. Chem.* **2004,** 47(24) 5972–5983.

[18] 18.Rostom, S. A.and Abd El Razik, H. A.; *Arch. Pharm.* **2009,** 344, 572-587.

[19] 19.Ahmed, O. M and Ahmed, S. A.; *Eur. J. Med. Chem.* **2009,** *44,* 3519-3523.

[20] 20.Rashad, A. and Abdel-Megeid, M. E. *J. Heterocy. Chem.* **2005,** *16(3),* 226–234.

[21] Shah, R. D. *Molecules* **2002,** *7,* 554-556.

[22] Rajasekaran, A. and Thampi, P. P.; *Eur. J. Med. Chem.* **2004,** *39,* 273–279.

[23] Kozikowski, A. P.; Zhang, J.; Nan, F.; Petukhov, A.; Grajkowska, E.; Wroblewski, J. T.; Yamamoto, T.; Bzdega, T.; Wroblewska, B. and Neale, J. H.; *J. Med. Chem.* **2004,** *47,*1729–1738.

[24] Upadhayaya, R.; Jain, S.; Sinha, N.; Kishore, N.; Chandra, R. and Arora, S. K.; "Synthesis of nove l substituted tetrazoles having antifungal activity" *Eur. J. Med. Chem. 39,* **2004,** 579–592.

[25] Zarubaev, V. V.; Golod, E. L.; Anfimov, P. M.; Shtro, A. A.; Saraev, V. V.; Gavrilov, A. S.; Logvinov, A. V. and Kiselev, O. I.; *Bioorg. Med. Chem.* **2010,** *18,* 839-848.