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Synthesis of Diverse 1, 2, 4-Triazolo[1,5-A]Pyrimidine Derivatives

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ABSTRACT

Microwave assisted organic synthesis has become an important tool to medicinal chemists for rapid organic synthesis. The biological importance of 1,2,4-triazolo[1,5-a]pyrimidines is well reported. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. Keeping in mind these facts, microwave assisted synthesis of 1,2,4-triazolo[1,5-a]pyrimidines has been undertaken. The structures of all the newly synthesized compounds are elucidated by FT-IR, mass spectra, ^{1}H NMR and elemental analysis.

Keywords : Microwave assisted organic synthesis, 1,2,4-triazolo[1,5-a]pyrimidines, FT-IR, mass spectra, ^{1}H NMR

I. INTRODUCTION

Microwave energy, originally applied for heating foodstuffs by Percy Spencer in the 1940s, has found a variety of technical applications in the chemical and related industries since the 1950s, in particular in the food-processing, drying and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing and extraction) [1] to biochemistry (protein hydrolysis, sterilization) [1], pathology (histoprocessing, tissue fixation) [2] and medical treatments (diathermy) [3]. Somewhat surprisingly, microwave heating has only been implemented in organic synthesis since the mid-1980s. The first reports on the use of microwave heating to accelerate organic chemical transformations (MAOS) were published by the groups of Richard Gedye [4] and Raymond J. Giguere/George Majetich [5] in 1986.

The cyclocondensation of a ring of 1,2,4-triazole and another one of pyrimidine forms bicyclic heterocycles known as 1,2,4-triazolopyrimidines. It can exist in four different orientation due to different attachments of both the rings that give rise to four isomeric structures; 1,2,4-triazolo[1,5-a]pyrimidine, 1,2,4-triazolo[1,5-c]pyrimidine, 1,2,4-triazolo[4,3-a]pyrimidine and 1,2,4-triazolo[4,3-c]pyrimidine. Among these family 1,2,4-triazolo[1,5-a]pyrimidine derivatives is more stable thermodynamically as compare to others and thus it explored most [6]. Revisions surveying the synthesis, reactivity, spectroscopic characterization and crystallographic studies of 1,2,4-triazolo[1,5-c]pyrimidines [7], 1,2,4-triazolo[4,3-a]pyrimidines [8] and 1,2,4-triazolo[4,3-c]pyrimidines [9] have also been published.

As far as biological activity is concerned, fused heteroaromatic scaffolds are often of ample greater interest than the constituent monocyclic compounds. Recently, 1,2,4-triazolo[1,5-a]pyrimidines have aroused snowballing attention from the chemical and biological view points, due to their diverse pharmacological activities, such as antitumor potency [10, 11], inhibition of KDR kinase [12], antifungal effect [13] and macrophage activation [14]. They have proved to be promising anticancer agents with dual

mechanisms of tubulin polymerization promotion [10, 11] as well as cyclin dependent kinases 2 inhibition [15]. Some examples of published derivatives of 1,2,4-triazolo[1,5-a]pyrimidine with their biological activities are as following.

II. EXPERIMENTAL

Materials and method

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. Microwave assisted reaction were carried out in QPro-M microwave synthesizer. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. 1H NMR was determined in DMSO-d6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

General procedure for the synthesis of (5-methyl-7-(substituted phenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)(phenyl)methanone (4a-t)

A mixture of the aminoazole (0.01 mol), 1-(substituted)phenylbutane-1,3-dione (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in ethanol (5 mL) was irradiated under microwave conditions at 120 °C for 10-12 min. The microwave irradiation was operated in 30-second cycles. The reaction mixture was allowed to stand overnight at room temperature and was then filtered to give the solid triazolopyrazolopyrimidine products 4a-t, which were washed with ethanol and dried in air. Triazolopyrimidines were obtained in high purity and did not require further purification by recrystallization.

(4-methoxyphenyl)(7-(4-methoxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimi- din-6-yl)methanone (4a)

Yield: 76%; mp 218-220 ºC; IR (cm-1): 3269 (N-H stretching of secondary amine), 3024 (C-H stretching of aromatic ring), 2922 (C-H asymmetrical stretching of CH_3 group), 2868 (C-H asymmetrical stretching of CH_3 group), 1666 (C=O stretching of carbonyl group), 1618 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1510, 1479 and 1442 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH_3 group), 1329 (C-H symmetrical deformation of CH_3 group), 1280 (C-N stretching), 1247 (C-O-C stretching), 1033 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.26 (s, 3H), 3.56 (s, 3H), 3.79 (s, 3H), 6.59 (s, 1H), 6.76-6.78 (d, 2H, J = 8.84 Hz), 6.96-7.00 (t, 2H), 7.32-7.38 (m, 4H), 7.57 (s, 1H), 11.06 (s, 1H); MS: m/z 376.

(7-(4-fluorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)(4-methoxy-phenyl)methanone (4b)

Yield: 70%; mp 226-228 ºC; IR (cm-1): 3230 (N-H stretching of secondary amine), 3115 (C-H symmetrical stretching of CH_3 group), 2937 (C-H asymmetrical stretching of CH_3 group), 1712 (C=O stretching of carbonyl group), 1641 (C=N stretching of triazole ring), 1525 and 1483 (C=C stretching of aromatic ring), 1435 (C-H asymmetrical deformation of CH_3 group), 1408 (C-N-C stretching of pyrimidine ring), 1340 (C-H symmetrical deformation of CH_3 group), 1276 (C-N stretching of pyrimidine ring), 1240 (C-O-C asymmetrical stretching of ether linkage), 1174 (C-H in plane deformation of aromatic ring), 1062 (C-O-C symmetrical stretching of ether linkage), 866 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d6) δ ppm: 2.24 (s, 3H), 3.50 (s, 3H), 6.42 (s, 3H), 6.93-6.95 (d, 2H, J = 8.4 Hz), 7.03-7.09 (m, 4H), 7.71-7.73 (m, 3H), 11.29 (s, 1H); MS: m/z 364.

(4-methoxyphenyl)(5-methyl-7-(p-tolyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)- methanone (4c)

Yield: 78%; mp 198-200 ºC; IR (cm-1): 3259 (N-H stretching of secondary amine), 3032 (C-H stretching of aromatic ring), 2920 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H asymmetrical stretching of CH_3 group), 1668 (C=O stretching of carbonyl group), 1606 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1514 and 1480 (C=C stretching of aromatic ring), 1440 (C-H asymmetrical deformation of CH_3 group), 1410 (C-H symmetrical deformation of CH_3 group), 1330 (C-N stretching), 1247 (C-O-C stretching), 1028 (C-H in plane deformation of aromatic ring), 821 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.19 (s, 3H), 3.80 (s, 3H), 6.28 (s, 1H), 6.85-6.87 (d, 2H, J = 8.80 Hz), 6.94-6.97 (d, 2H, J = 9.20 Hz), 7.03-7.05 (d, 2H, J = 8.00 Hz), 7.71-7.74 (d, 3H), 11.26 (s, 1H); MS: m/z 360.

(4-methoxyphenyl)(5-methyl-7-(4-nitrophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)methanone (4d)

Yield: 72%; mp 226-228 ºC; IR (cm-1): 3225 (N-H stretching of secondary amine), 3119 (C-H symmetrical stretching of CH_3 group), 2940 (C-H asymmetrical stretching of CH_3 group), 1717 (C=O stretching of carbonyl group), 1644 (C=N stretching of triazole ring), 1530 and 1490 (C=C stretching of aromatic ring), 1440 (C-H asymmetrical deformation of CH_3 group), 1410 (C-N-C stretching of pyrimidine ring), 1350 (C-H symmetrical deformation of CH_3 group), 1280 (C-N stretching of pyrimidine ring), 1255 (C-O-C asymmetrical stretching of ether linkage), 1180 (C-H in plane deformation of aromatic ring), 1065 (C-O-C symmetrical stretching of ether linkage), 870 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d6) δ ppm: 2.30 (s, 3H), 3.56 (s, 3H), 6.44 (s, 3H), 6.90-6.94 (d, 2H, J = 8.3 Hz), 7.06-7.12 (m, 4H), 7.74-7.77 (m, 3H), 11.25 (s, 1H); MS: m/z 391.

(7-(4-chlorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)(4-methoxyphenyl)methanone (4e)

Yield: 76%; mp 240-242 ºC; 3217 (N-H stretching of secondary amine), 3045 (C-H stretching of aromatic ring), 2964 (C-H asymmetrical stretching of CH_3 group), 2872 (C-H asymmetrical stretching of CH_3 group), 1666 (C=O stretching of carbonyl group), 1595 (C=N stretching of triazole ring), 1516 (N-H deformation of pyrimidine ring), 1440, 1400 (C=C stretching of aromatic ring), 1411 (C-H asymmetrical deformation of CH_3 group), 1344 (C-H symmetrical deformation of CH_3 group), 1280 (C-N stretching), 1247 (C-O-C stretching), 1033 (C-H in plane deformation of aromatic ring), 819 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.25 (s, 3H), 3.85 (s, 3H), 6.39 (s, 3H), 6.95-6.97 (d, 2H, J = 8.40 Hz), 7.07-7.09 (d, 2H, J = 8.00 Hz), 7.30-7.32 (d, 2H, J = 8.00 Hz), 7.74-7.80 (m, 3H), 11.36 (s, 1H); MS: m/z 380.

(7-(3-chlorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)(4-methoxyphenyl)methanone (4f)

Yield: 70%; mp 243-245 ºC; 3211 (N-H stretching of secondary amine), 3041 (C-H stretching of aromatic ring), 2961 (C-H asymmetrical stretching of CH_3 group), 2869 (C-H asymmetrical stretching of CH_3 group), 1661 (C=O stretching of carbonyl group), 1591 (C=N stretching of triazole ring), 1511 (N-H deformation of pyrimidine ring), 1435, 1395 (C=C stretching of aromatic ring), 1405 (C-H asymmetrical deformation of CH_3 group), 1341 (C-H symmetrical deformation of CH_3 group), 1275 (C-N stretching), 1241 (C-O-C stretching), 1026 (C-H in plane deformation of aromatic ring), 811 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.24 (s, 3H), 3.80 (s, 3H), 6.35 (s, 3H), 6.92-6.95 (d, 2H, J = 8.40 Hz), 7.02-7.04 (d, 2H, J = 8.00 Hz), 7.26-7.29 (d, 2H, J = 8.00 Hz), 7.71-7.75 (m, 3H), 11.30 (s, 1H); MS: m/z 380.

(4-methoxyphenyl)(5-methyl-7-(3-nitrophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)methanone (4g)

Yield: 72%; mp 237-239 ºC; 3213 (N-H stretching of secondary amine), 3043 (C-H stretching of aromatic ring), 2963 (C-H asymmetrical stretching of CH_3 group), 2871 (C-H asymmetrical stretching of CH_3 group), 1663 (C=O stretching of carbonyl group), 1593 (C=N stretching of triazole ring), 1513 (N-H deformation of pyrimidine ring), 1438, 1398 (C=C stretching of aromatic ring), 1408 (C-H asymmetrical deformation of CH_3 group), 1345 (C-H symmetrical deformation of CH_3 group), 1277 (C-N stretching), 1244 (C-O-C stretching), 1029 (C-H in plane deformation of aromatic ring), 817 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.27 (s, 3H), 3.83 (s, 3H), 6.39 (s, 3H), 6.96-6.99 (d, 2H, J = 8.40 Hz), 7.08-7.11 (d, 2H, J = 8.00 Hz), 7.31-7.34 (d, 2H, J = 8.00 Hz), 7.75-7.78 (m, 3H), 11.22 (s, 1H); MS: m/z 391.

(7-(2-chlorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)(4-methoxy-phenyl)methanone (4h)

Yield: 64%; mp 236-238 ºC; 3218 (N-H stretching of secondary amine), 3048 (C-H stretching of aromatic ring), 2968 (C-H asymmetrical stretching of CH_3 group), 2878 (C-H asymmetrical stretching of CH_3 group), 1669 (C=O stretching of carbonyl group), 1599 (C=N stretching of triazole ring), 1518 (N-H deformation of pyrimidine ring), 1445, 1405 (C=C stretching of aromatic ring), 1414 (C-H asymmetrical deformation of CH_3 group), 1351 (C-H symmetrical deformation of CH_3 group), 1281 (C-N stretching), 1250 (C-O-C stretching), 1034 (C-H in plane deformation of aromatic ring), 821 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.24 (s, 3H), 3.81 (s, 3H), 6.40 (s, 3H), 6.92-6.95 (d, 2H, J = 8.40 Hz), 7.10-7.14 (d, 2H, J = 8.00 Hz), 7.34-7.38 (d, 2H, J = 8.00 Hz), 7.81-7.84 (m, 3H), 11.13 (s, 1H); MS: m/z 380.

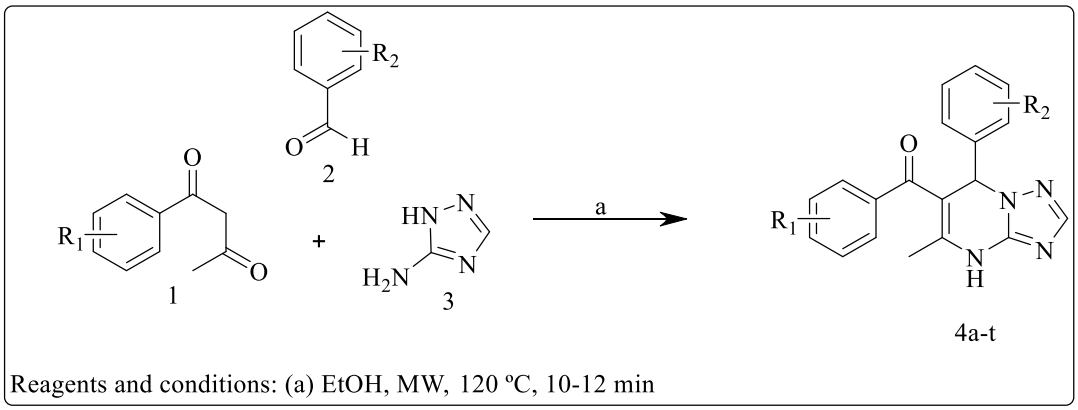
(4-methoxyphenyl)(5-methyl-7-(2-nitrophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)methanone (4i)

Yield: 61%; mp 244-246 ºC; 3225 (N-H stretching of secondary amine), 3055 (C-H stretching of aromatic ring), 2975 (C-H asymmetrical stretching of CH_3 group), 2885 (C-H asymmetrical stretching of CH_3 group), 1675 (C=O stretching of carbonyl group), 1605 (C=N stretching of triazole ring), 1526 (N-H deformation of pyrimidine ring), 1451, 1411 (C=C stretching of aromatic ring), 1419 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1286 (C-N stretching), 1256 (C-O-C stretching), 1039 (C-H in plane deformation of aromatic ring), 827 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.21 (s, 3H), 3.87 (s, 3H), 6.44 (s, 3H), 6.96-6.98 (d, 2H, J = 8.40 Hz), 7.12-7.13 (d, 2H, J = 8.00 Hz), 7.36-7.39 (d, 2H, J = 8.00 Hz), 7.83-7.85 (m, 3H), 11.17 (s, 1H); MS: m/z 391.

(4-methoxyphenyl)(7-(2-methoxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimi- din-6-yl)methanone (4j)

Yield: 59%; mp 245-247 ºC; 3228 (N-H stretching of secondary amine), 3059 (C-H stretching of aromatic ring), 2980 (C-H asymmetrical stretching of CH_3 group), 2891 (C-H asymmetrical stretching of CH_3 group), 1682 (C=O stretching of carbonyl group), 1613 (C=N stretching of triazole ring), 1535 (N-H deformation of pyrimidine ring), 1461, 1421 (C=C stretching of aromatic ring), 1430 (C-H asymmetrical deformation of CH_3 group), 1358 (C-H symmetrical deformation of CH_3 group), 1288 (C-N stretching), 1259 (C-O-C stretching), 1043 (C-H in plane deformation of aromatic ring), 832 (C-H out of plane bending of 1,4-disubstituion); ^{1}H NMR (DMSO-d6) δ ppm: 2.27 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 6.46 (s, 3H), 6.99-4.01 (d, 2H, J = 8.40 Hz), 7.16-7.18 (d, 2H, J = 8.00 Hz), 7.32-7.35 (d, 2H, J = 8.00 Hz), 7.86-7.88 (m, 3H), 11.20 (s, 1H); MS: m/z 376.

Reaction Scheme



Reagents and conditions: (a) EtOH, MW, 120 ºC, 10-12 min

Table 1. Physical data of synthesized compounds

Code	R_1	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	4-OCH_3	4-OCH_3	$C_{21}H_{20}N_4O_3$	376	218-220	76	0.54	0.71
4b	4-OCH_3	4-F	$C_{20}H_{17}FN_4O_2$	364	226-228	70	0.50	0.69
4c	4-OCH_3	4-CH_3	$C_{21}H_{20}N_4O_2$	360	198-200	78	0.49	0.64
4d	4-OCH_3	4-NO_2	$C_{20}H_{17}N_5O_4$	391	226-228	72	0.52	0.68
4e	4-OCH_3	4-Cl	$C_{20}H_{17}ClN_4O_2$	380	240-242	76	0.54	0.70
4f	4-OCH_3	3-Cl	$C_{20}H_{17}ClN_4O_2$	380	243-245	70	0.46	0.74
4g	4-OCH_3	3-NO_2	$C_{20}H_{17}N_5O_4$	391	237-239	72	0.50	0.70
4h	4-OCH_3	2-Cl	$C_{20}H_{17}ClN_4O_2$	380	236-238	64	0.49	0.63
4i	4-OCH_3	2-NO_2	$C_{20}H_{17}N_5O_4$	391	244-246	61	0.42	0.62
4j	4-OCH_3	2-OCH_3	$C_{21}H_{20}N_4O_3$	376	245-247	59	0.48	0.74

III. RESULTS AND DISCUSSION

The biological importance of 1,2,4-triazolo[1,5-*a*]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. For example, they have demonstrated activity against malaria and bronchospasm and shown activity as coronary vasodilators, antihypertensive agents, leishmanicides, antibiotics, adenosine A_{2a} antagonists, immunosuppressants, antitumor agents, fungicides, xanthine oxidase inhibitors, and phosphodiesterase inhibitors.

One of the synthetic pathways to 1,2,4-triazolo[1,5-*a*]pyrimidines is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with aminoazoles containing a guanidine fragment. There are literary data about the synthesis of triazolopyrimidines by treatment of 5-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and ethyl acetoacetate or cyclic *β*-diketones. The cyclocondensations were realized by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions or using DMF as solvent. The use of 1-phenylbutane-1,3-dione in these or similar reactions has not been described at much extent. Recognizing these facts, we have synthesised four new series of 1,2,4-triazolo[1,5-*a*]pyrimidines (4a-t) containing 1-phenylbutane-1,3-dione fragment. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, and ^{1}H NMR spectroscopy.

IV. CONCLUSION

The present paper describes applications of microwaves in heterocyclic ring formation. Recently, 1,2,4-triazolo[1,5-*a*]pyrimidines have aroused increasing from the standpoint of biological activity, due to their diverse pharmacological activities. It includes synthesis of forty novel 1,2,4-triazolo[1,5-*a*]pyrimidines and brief review of the reported synthetic strategies. Forty 1,2,4-triazolo[1,5-*a*]pyrimidines were synthesized by one-pot, microwave-assisted condensation reaction of aromatic aldehyde, corresponding 1-phenylbutane-1,3-dione and 5-amino-1,2,4-triazole using ethanol as a solvent. Thus, a new green chemistry approach was developed leading to the improvement in the reaction time, yield and simplicity of work up procedure.

V. REFERENCES

[1]. Kingston, H. M.; Haswell S. J. (Eds.) Microwave-Enhanced Chemistry. Fundamentals, Sample preparation and Applications, American Chemical Society, Washington DC, 1997.

[2]. Giberson, R. T.; Demaree R. S. (Eds.) Microwave Techniques and Protocols, Humana Press, T otowa, New Jersey, 2001.

[3]. Prentice, W. E. Therapeutic Modalities for Physical Therapists, McGraw-Hill, New York, 2002.

[4]. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Lett. 1986, 27, 279.

[5]. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. Tetrahedron Lett. 1986, 27, 4945.

[6]. Fischer, G. Adv. Heterocycl. Chem. 1993, 57, 81.

[7]. Shaban, M.A.E.; Morgan, A.E.A. Adv. Heterocycl. Chem. 2000, 77, 345.

[8]. Shaban, M.A.E.; Morgan, A.E.A. Adv. Heterocycl. Chem. 2000, 73, 131.

[9]. Shaban, M.A.E.; Morgan, A.E.A. Adv. Heterocycl. Chem. 2000, 75, 243.

[10]. Zhang, N.; Semiramis, A. K.; Thai N. et al. J. Med. Chem. 2007, 50, 319.

[11]. Havlicek, L.; Fuksova, K.; Krystof, V. et al. Bioorg. Med. Chem. 2005, 13, 5399.

[12]. Fraley M. E., Hoffman W. F., Rubino R. S. Bioorg. Med. Chem. Lett. 2002, 12, 2767.

[13]. Chen, Q.; Zhu, X. L.; Liu, Z. M. et al. Eur. J. Med. Chem. 2008, 43, 595.

[14]. Uryu, S.; Tokuhiro, S.; Murasugi, T. et al. Brain Research 2002, 946, 298

[15]. Fairfield, B. J.; Andrew, C.; Allan, J. WO2004108136, 2004.