Research Journal of Recent Sciences _____ ISSN 2277 - 2502
Vol. **1(ISC-2011),** 105-109 **(2012)** *Res.J.Recent.Sci.*

Microwave assisted synthesis of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1, 3, 5-triazine-2, 4 (1H, 3H)-dione derivatives Under solvent free condition with high yields

Yaddanapudi Prabhakar, Kottapalli R S Prasad and Jagarlapudi V S Kumar
Department of Chemistry, K. L. University, Vaddeswaram, Andhra Pradesh, INDIA
Available online at: www.isca.in
(Received 27th November 2011, revised 31th December, accepted 24th January 2012)

Abstract

A simple and highly efficient procedure has been described for the synthetic derivatives of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H, 3H)-dione under solvent free condition at microwave power 400 W using domestic microwave. The structures of synthesised compounds are confirmed by using spectral studies.

Keywords: Synthesis, microwave irradiation, heterocyclic compounds and spectral studies.

Introduction

Microwave assisted organic synthesis has become a field of increasing interest in the use of environmentally safe conditions. Microwave irradiation provides a way for flash heating as an alternative to standard thermal heating in chemical reactions. This technology has been employed to drastically reduce reaction times and even modify selectivity. In addition to this feature, the use of microwave irradiation may outperform conventional reaction conditions in other aspects, such as easier workup, reduction of the usual thermal degradation products, reduction of toxic and expensive quantities of solvents (green chemistry), and reduction of secondary products. Also, microwave irradiation has proven to be of benefit particularly for reactions under dry media (i.e. in the absence of solvents or solid support) and reactions without catalysts.

Recent advances in the technology have now made microwave energy a more efficient means of heating reaction. The use of microwave irradiation has introduced several new concepts in chemistry, since the absorption and transmission of the energy is completely different from the conventional mode of heating. Particularly, reactions involving a heterogeneous mixture of the two neat reactants can eventually lead to a clean, efficient and be more economical.

Microwave irradiation has become a very useful tool in organic synthesis and has been used to enhance a great number of classical reactions in the last 20 years due to the advantages they provide over conventional heating methods. So we designed solvent free microwave assisted synthesis of 3-(4-Ethylbenzyl)-1- (4-methoxybenzyl)-6-(methylthio)-1, 3, 5-triazine-2,4(1H, 3H)-dione derivatives[1-4].

Material and Methods

Bv8 is a small protein secreted by frog's skin. Mammalian homologues of Bv8 (Bombina variegata molecular mass ~8 kDa) the prokinetician receptor PK1 and PK2, and their G-protein coupled receptors PKR1 and PKR2 have been identified and linked to several biological effects[6, 8, 9, 11]. Triazine compounds as antagonists at Bv8prokinetician receptors, we proposed a convenient and solvent free microwave assisted synthetic approach for 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H, 3H)-dione derivatives[1, 2, 3, 4, 5, 7, 12].

First three steps are synthesised in reported procedures and we got consistent yields to the reported method. But in the step-4 we faced a solubility issue of triazine compound. Because of this reason we end up with poor yields. So we look forward for the better synthetic procedure. We found 4-bromobenzene sulfonyl chloride as one of the better leaving groups in substitution reactions. Fist we coupled with 4-bromo benzenesulfonyl chloride with 4-ethyl benzyl alcohol then we did a substitution reaction with triazine compound. We got yield of 76% with high purity with microwave irradiation at 70^0C (400W) with in 0.5 h. This result made us to think of microwave assisted synthesis of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H, 3H)-dione derivatives.

Microwave irradiation reduces the reaction time at the maximum and avoids other unwanted side reactions. Solvent free conditions reduce lot of synthetic process and also environmentally safe. Purification of these types of reactions makes much easier than the conventional reactions. High recovery of unreacted raw materials is the major advantage in solvent free conditions which gives economical synthetic approach. Here majorly we synthesised triazine derivatives by substituting "-SMe" with primary amine group.

Conventional route is taking 8 h time for the complete conversion of starting compound to product but in microwave irradiation we synthesised same compound within 5 min. This result has given good support for our basic idea. We synthesised few derivatives, but all the derivatives gave above 90% yield and a complete recovery of unreacted starting material.

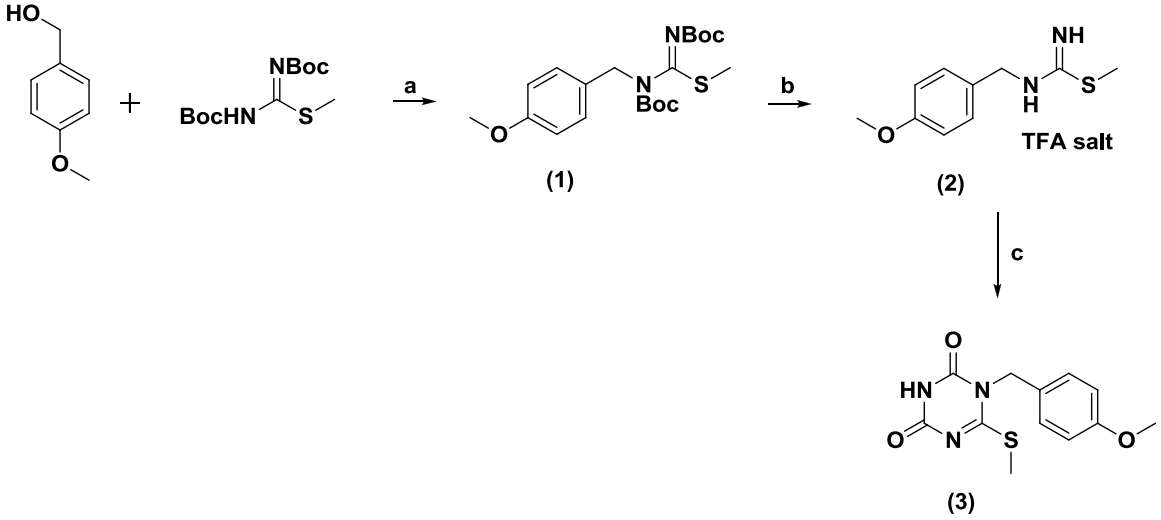


Figure -1
THF, DEAD, PPh_3, room temp. Y =70%; (b) TFA, room temp. Y = 97%; (c) Dichloromethane, chlorocarbonyl isocyanate, N,N-diisopropylethylamine, 18 h, Y = 30%.Synthesis of 1-(4-Methoxybenzyl) -6-(methylthio)-1, 3,5-triazine-2,4(1H, 3H)-dione

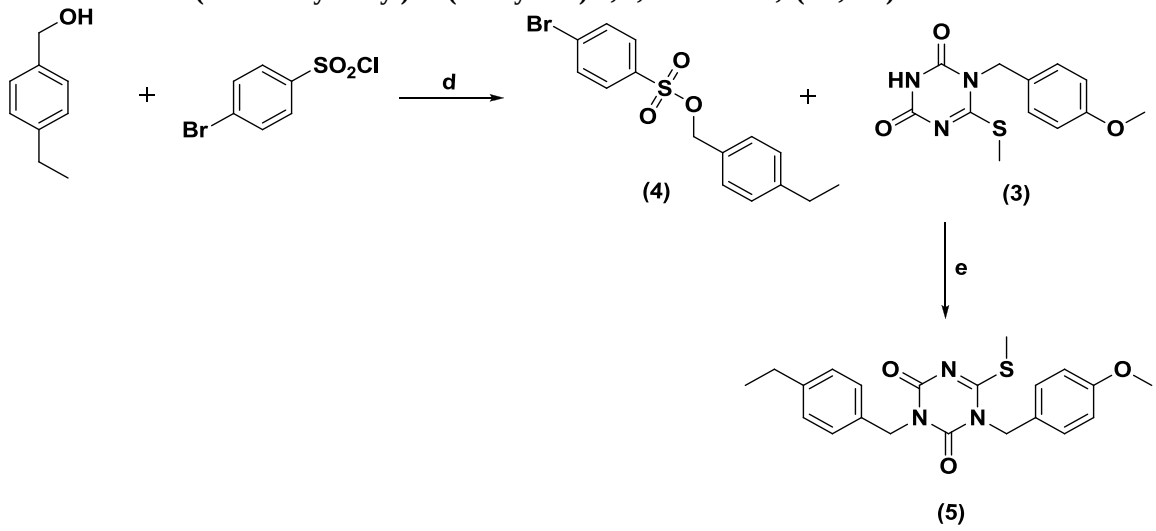


Figure -2
(d) N,N-diisopropylethylamine, N,N-dimethylaminopyridine, dichloromethane, room temperature, 18 h. (e) Cs_2CO_3, DMF, 70^0C, Microwave, 0.5 h .Y=72%
Synthesis of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6- (methylthio)-1,3,5-triazine-2,4(1H,3H)-dione

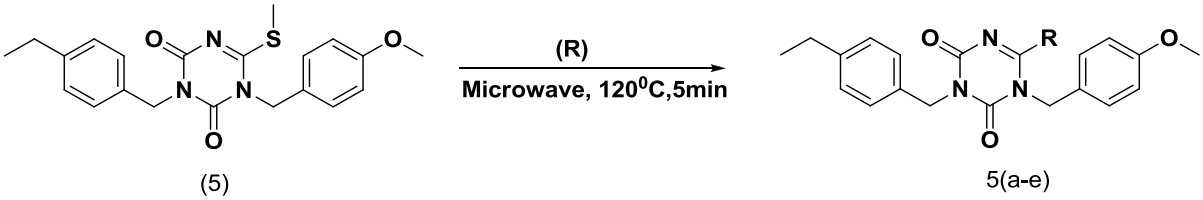
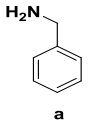
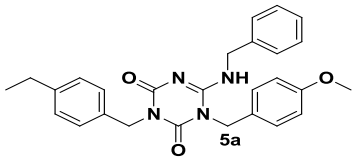
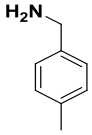
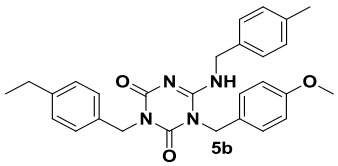
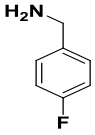
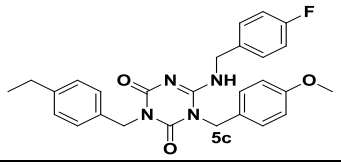
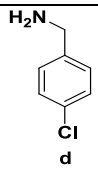
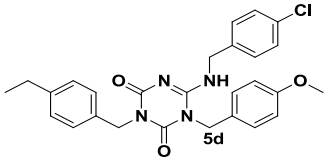
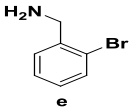
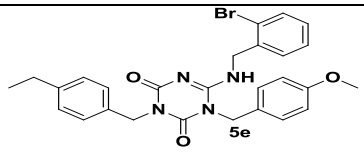


Figure -3
Microwave assisted synthesis of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1, 3, 5- triazine-2,4(1H, 3H)-dione derivatives.

Table-1
List of substituted aromatic primary amines (R) used for the derivatisation process and the obtained products

S. No.	(R)	Product	Yield (%)
1	 a	 5a	97
2	 b	 5b	95
3	 c	 5c	93
4	 d	 5d	98
5	 e	 5e	96

Results and Discussion

We followed the synthetic procedure for 1-(4-Methoxybenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H, 3H)-dione[4]. Even for compound (5) also we tried to follow but because of solubility issue with compound (3) we got very poor yield. So we tried to make –OH as good leaving group by coupling with 4-bromobenzenesulfonylchloride and substitution with compound (3) then we got good yield (72%). But in a conventional route it took 18 h to complete starting material. Same conditions, we tried in microwave to reduce reaction time, strangely starting material was consumed in 0.5 h and with same yield as conventional. "–SMe" is one of the better leaving groups in organic chemistry. Based on this logic we prepared derivatives of compound (5). Substituted benzyl amines are taken for this process because these are liquid in nature, so it helps in solvent free synthesis. When we took compounds (a-e) and compound (5) in a microwave vial, homogeneous solution appeared. After 5 min microwave irradiation at 120^0C compound (5) was consumed. Crude as it is was purified by silica gel column chromatography without any workup. Unreacted compounds (a-e) were recovered.

Experimental procedure: 1,3-Bis-(tert-butoxycarbonyl)-1-(4-methoxybenzyl)-2-methyl-3-thiopseudourea (1): To a solution of 1,3- bis(tert-butoxycarbonyl)- 2 – methyl – 2 - thiopseudourea (2.0 g, 6.90 mmol), 4-methoxybenzyl alcohol (0.94 mL, 7.59 mmol) and triphenylphosphine (1.99 g, 7.59 mmol), at 0^0C in anhydrous THF, was added solution of diethyl azodicarboxylate (1.4 mL, 7.59 mmol) dissolved in anhydrous THF. After 10 min, the reaction was warmed to room temperature and stirred for 18 h. The solvent was removed under vacuum, and the crude intermediate was purified by flash chromatography (EtOAc/Petether, 1:9, v/v): yield 2.04 g (72%); m/z 411 (M + H)+. ^{1}H NMR ($CDCl_3$): δ 7.29-7.28 (d, 2H, J= 8.4 Hz), 6.87-6.86 (d, 2H, J = 8.4 Hz), 4.73 (s, 2H), 3.81 (s, 3H), 2.28 (s, 3H), 1.54 (s, 9H), 1.44 (s, 9H).

1-(4-Methoxy-benzyl)-2-methyl-3-thiopseudourea (2): Intermediate (1) (1.51 g, 3.68 mmol) was treated with TFA (10 mL) for 3 h. at room temperature. TFA was removed

under vacuum, crude was cooled to 0^0C and the deprotected intermediate was precipitated from Et_2O: yield 1.15 g (97%); m/z 211 (M +H)+. ^{1}H NMR (DMSO-d6): δ 9.17 (s,2H), 7.26-7.23(d, 2H, J=8.6), 6.95-6.92 (d, 2H, J=8.6), 4.47-4.45 (d, 2H, J=5.5), 3.73(s, 3H), 2.60 (s, 3H).

1-(4-Methoxybenzyl)-6-(methylthio)-1, 3,5- triazine,4(1H, 3H)-dione (3): To a solution of (2) (1.1 g, 3.57 mmol) in dichloromethane (20 mL) at 0^0C N,N-diisopropylethylamine (1.83 mL, 10.7 mmol) was added. At the same temperature, N-Chlorocarbonyl isocyanate (0.26 mL, 3.57 mmol), dissolved in dichloromethane (5 mL), was added drop wise. The reaction mixture was allowed to stir while slowly warming to room temperature (1 h) and was then stirred for an additional 24 h. The solvent was evaporated, and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with brine and dried over Na_2SO_4. The solution was filtered, the solvent evaporated, and the residual oil was precipitated from methanol: yield 0.276 g (30%); m/z 280 (M + H)+. ^{1}H NMR (DMSO-d6): δ 11.58 (bs, 1H), 7.23-7.20 (d, 2H, J= 8.7 Hz), 6.90-6.87 (d, 2H, J=8.7 Hz), 4.97 (s, 2H), 3.73 (s, 3H), 2.45 (s, 3H).

4-Ethylbenzyl 4-bromobenzenesulfonate (4) (Scheme-2): To a solution of (4-ethylphenyl)methanol (0.5 g, 3.67 mmol) in dichloromethane (10 mL) at 0^0C N,N-diisopropylethylamine (1.25 mL, 7.34 mmol) and N,N-dimethyl amino pyridine (0.089 g, 0.73 mmol) was added. After 10 min, 4-bromobenzenesulfonylchloride (1.03 g, 4.03 mmol) was added portion wise and stirred at room temperature for 18 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water, EtOAc layer was separated, washed with saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered and evaporated the solvent. Crude (1.2 g) was taken for the next step without any further purification.

3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1,3 ,5-triazine-2,4(1H, 3H)-dione (5) (Scheme-2): A solution of (4) (0.6 g crude), (3) (0.250 g, 0.89 mmol) and Cs_2CO_3 (0.583 g, 1.79 mmol) in dry DMF (3 mL) was subjected for microwave irradiation (400W) at 70^0C for 0.5 h. The reaction mass was diluted with ethyl acetate, filtered and evaporated the filtrate. Crude intermediate was purified by flash chromatography (EtOAc/Petether, 2:8, v/v); Yield=0.256 g (72%). m/z=(M+H)+=420. ^{1}H NMR (DMSO-d6): δ 7.24-7.20 (m, 4H), 7.15-7.12 (d, 2H, J=8Hz), 6.90-6.87 (d, 2H, J=8.6 Hz), 3.71 (s, 3H), 2.58-2.53 (q, 2H, J=7.5Hz), 2.46 (s, 3H), 1.15-1.10 (t, 3H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$): 169.84, 159.52, 152.19, 150.43, 143.91, 133.30, 129.39 (2 carbon atoms), 129.20 (2 carbon atoms), 127.88 (2 carbon atoms), 126.23, 114.05 (2 carbon atoms), 55.20, 47.93, 45.36, 28.49, 15.44, 15.23.

6-(Benzylamino)-3-(4-ethylbenzyl)-1-(4-methoxybenzyl)-1,3,5-triazine-2,4(1H, 3H)-dione (5a) (Scheme-3): The mixture of (5) (0.05 g, 0.12 mmol) and (a) (0.134 g, 1.25 mmol) in a vial stirred for 1 min and subjected to microwave irradiation (400W) at 120^0C for 5 min. Reaction mass was directly purified by flash chromatography (EtOAc/Petether, 4:6, v/v); yield=0.055 g (97%). m/z (M+H)+= 457. ^{1}H NMR ($CDCl_3$): δ 8.26 (bs, 1H), 7.26-7.19 (m, 7H), 7.13-7.08 (m, 4H), 6.91-6.89 (dd, 2H, J= 2.04Hz, 2.0Hz), 5.08 (s, 2H), 4.86 (s, 2H), 4.51-4.50 (d, 2H, J=4.6), 3.73 (s, 3H), 2.58-2.52 (q, 2H, J=7.6Hz), 1.16-1.12 (t, 3H, 7.5Hz). ^{13}C NMR ($CDCl_3$): 159.83,154.43, 153.87, 151.37, 143.59, 136.33, 134.08, 129.07 (2 carbon atoms), 128.69 (2 carbon atoms), 127.91 (3 carbon atoms), 127.81 (2 carbon atoms), 127.44 (2 carbon atoms), 125.64, 114.90 (2 carbon atoms), 55.29, 45.88, 45.37, 45.33, 28.49, 15.45.

3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(4-ethylbenzyla mino-1,3,5-triazine-2,4(1H,3H)-dione (5b) (Scheme-3): The mixture of (5) (0.05 g, 0.12 mmol) and (b) (0.152 g, 1.25 mmol) in a vial stirred for 1 min and was subjected to microwave irradiation (400W) at 120^0C for 5 min. Reaction mass directly purified by flash chromatography (EtOAc/Petether, 4:6, v/v); yield=0.056 g (95%). m/z(M+H)+= 471. ^{1}H NMR ($CDCl_3$): δ 8.22 (bs, 1H), 7.18-7.10 (m, 7H), 7.04-6.958 (m, 4H), 6.90-6.87 (d, 2H, 8.6Hz), 5.06 (s, 2H), 4.84 (s, 2H), 4.45-4.43 (d, 2H, 5.4Hz), 3.72 (s, 3H), 2.57-2.52 (q, 2H, 7.5Hz), 2.25 (s, 3H) 1.15-1.10 (t, 3H, 7.6Hz). ^{13}C NMR ($CDCl_3$): 159.79, 154.53, 153.84, 151.57, 143.56, 137.56, 134.12, 133.30, 129.33 (2 carbon atoms), 129.18 (2 carbon atoms), 127.94 (2 carbon atoms), 127.80 (2 carbon atoms), 127.46 (2 carbon atoms), 125.72, 114.85 (2 carbon atoms), 55.27, 45.69, 45.34, 45.28, 28.49, 21.0, 15.45.

3-(4-Ethylbenzyl)-6-(4-fluorobenzylamino)-1-(4-methoxy benzyl)-1,3,5-triazine-2,4(1H,3H)-dione (5c) (Scheme-3): The mixture of (5) (0.05 g, 0.12 mmol) and (c) (0.157 g, 1.25 mmol) in a vial stirred for 1 min and was subjected to microwave irradiation (400W) at 120^0C for 5 min. Reaction mass was directly purified by flash chromatography (EtOAc/Petether, 4:6, v/v); yield=0.055 g (93%). m/z(M+H)+= 475. ^{1}H NMR ($CDCl_3$): δ 8.28 (bs, 1H), 7.20-7.17 (m, 8H), 7.15-7.05 (m, 2H), 6.92-6.90 (d, 2H, J=8.6Hz), 5.07 (s, 2H), 4.86 (s, 2H), 4.49-4.48 (d, 2H, J=5.2Hz), 3.74 (s, 3H), 2.58-2.55 (q, 2H, J=7.5Hz), 1.16-1.13 (t, 3H, J=7.6Hz). ^{13}C NMR ($CDCl_3$): 159.75, 154.67, 153.90, 151.49, 143.64, 134.02, 132.41,132.36, 129.25, 129.15, 128.96 (2 carbon atoms), 127.99 (2 carbon atoms), 127.82 (2 carbon atoms), 125.78, 115.57, 115.28, 114.74 (2 carbon atoms), 55.26, 45.36, 45.14, 44.87, 28.47, 15.44.

6-(4-Chlorobenzylamino)-3-(4-ethylbenzyl)-1 (4methoxy benzyl)-1,3,5-triazine-2,4(1H,3H)-dione (5d) (Scheme-3): The mixture of (5) (0.05 g, 0.12 mmol) and (d) (0.178 g, 1.25 mmol) in a vial stirred for 1min and was subjected to microwave irradiation (400W) at 120^0C for 5 min. Reaction mass was directly purified by flash chromatography (EtOAc/Petether, 4:6, v/v); yield=0.060 g (98%).

m/z(M+H)+ =491. ^{1}H NMR ($CDCl_3$): δ 7.42-7.40 (d, 2H), 7.16-7.09 (m, 6H), 6.86-6.82 (m, 4H), 5.72 (bs, 1H), 5.06-5.04 (d, 4H, J=6.4Hz), 4.44-4.42 (d, 2H, 4.9Hz), 3.79 (s, 3H), 2.66-2.60 (q, 2H, 7.4Hz),1.26-1.22 (t, 3H, 7.5Hz). ^{13}CNMR($CDCl_3$): 159.78, 154.60, 153.94, 151.47, 143.66, 135.09, 133.50, 128.99 (2 carbon atoms), 128.76 (2 carbon atoms), 128.70, 128.53, 128.40, 127.96 (2 carbon atoms), 127.83 (2 carbon atoms), 125.71, 114.78 (2 carbon atoms), 55.29, 45.38, 45.17, 44.86, 28.48, 15.46.

6-(2-Bromobenzylamino)-3-(4-ethylbenzyl)-1-(4-methoxy benzyl)-1,3,5-triazine-2,4(1H,3H)-dione (5e) (Scheme-3): The mixture of (5) (0.05 g, 0.12 mmol) and (e) (0.234 g, 1.25 mmol) in a vial stirred for 1 min and was subjected to microwave irradiation (400W) at 120^{0}C for 5 min. Reaction mass directly purified by Flash chromatography (EtOAc/Petether, 4:6, v/v); yield=0.064 g (96%). m/z(M+H)+ 535. ^{1}H NMR ($CDCl_3$): δ 7.46-7.41 (m, 3H), 7.18-7.14 (t, 7H, J=6.4Hz), 6.85-6.83 (d, 2H, J=8.6Hz)), 5.95-5.92 (t, 1H, J=5.0Hz), 5.04-5.02 (d, 4H, J=7.4Hz), 4.58-4.56 (d, 2H, J=5.4Hz), 3.79 (s, 3H), 2.65-2.59 (q, 2H, J=7.5Hz), 1.23-1.20 (t, 3H, J=7.6Hz).

^{13}C NMR ($CDCl_3$): 159.77, 154.59, 154.05, 151.56, 143.59, 135.79, 134.05, 132.60, 130.62, 129.47, 129.07 (2 carbon atoms), 128.09, 127.8, 127.71 (2 carbon atoms), 127.64, 125.68, 123.58, 114.79 (2 carbon atoms), 55.29, 45.76, 45.39, 45.36, 28.48, 15.47.

Conclusion

In conclusion, we have synthesised a series of 3-(4-Ethylbenzyl)-1-(4-methoxybenzyl)-6-(methylthio)-1, 3, 5-triazine-2,4(1H, 3H)-dione derivatives in very short time with high yield. Our main interest is to show that solvent free synthesis is environmentally safe and economical. Microwave irradiation in synthetic chemistry saves lot of time consumptions where you have option to use. Experimental protocol is easily accessible on milligram to gram scale.

Acknowledgements

The authors are thankful to the management of K. L. University for providing necessary facilities, which helped in concluding present work successfully.

References

1. Coats S.J., Dyatkin A. B., He W. Lisko J., Ralbovsky J. L. and Schultz M. J., Prokineticin 1 receptor antagonists, Patent WO2006104715 **(2006)**
2. Coats S.J., Dyatkin A. B., He W. Lisko J., Ralbovsky J. L. and Schultz M.J., Pyrimidindione derivatives as prokineticin 2 receptor antagonists, Patent WO2006104713 **(2006)**
3. Coats S. J., Dyatkin A. B., He W., Lisko J. and Miskowski T. A. Ralbovsky J. L. and Schultz M. J. Prokineticin 2 receptor antagonists, Patent WO2007079214 **(2007)**
4. Gianfranco B., Ilaria L., Claudio T., Lucia N., Roberta L., Elisa G., Annalisa N., Pietro M. and Sergio V. Chiara De N. and Severo S., Triazine Compounds as Antagonists at Bv8-Prokineticin Receptors, *J. Med. Chem.*, **51**, 7635–7639 **(2008)**
5. Kaser A., Winklmayr M., Lepperdinger G. and Kreil G. The AVIT protein family, Secreted cysteine-rich vertebrate proteins with diverse functions, *EMBO Rep.*, **4**, 469–473 **(2003)**
6. LeCouter J., Kowalski J., Foster J., Hass P., Zhang Z., Dillard-Telm L., Frantz G., Angell L., Deguzman L., Keller G., Peale F., Gurney A., Hillan K.J. and Ferrara N., Identification of an angiogenic mitogen selective for endocrine gland endothelium, *Nature*, **412**, 876–884 **(2001)**
7. Mollay C., Wechselberger C., Mignogna G., Negri L., Melchiorri P., Barra D. and Kreil G., Bv8, a small protein from frog skin and its homologue from snake venom induce hyperalgesia in rats, *Eur. J. Pharmacol.*, **374**, 189–196 **(1999)**
8. Negri L., Lattanzi R., Giannini E. and Melchiorri, P., Bv8/Prokineticin proteins and their receptors, *Life Sci.*, **81**, 1103–1116 **(2007)**
9. Negri L., Lattanzi R., Giannini E., Colucci M., Margheriti F., Melchiorri P., Vellani V., Tian H., De Felice M. and Porreca F., Impaired nociception and inflammatory pain sensation in mice lacking the prokineticin receptor PKR1, focus on interaction between PKR1 and the capsaicin receptor TRPV1 in pain behaviour, *J. Neurosci.*, **26**, 6716–6727 **(2006)**
10. Negri L., Lattanzi R., Giannini E., Colucci M. A., Mignogna G., Barra D., Grohovaz F., Codazzi F., Kaiser A., Kreil G. and Melchiorri P., Biological activities of Bv8 analogues, *Br. J. Pharmacol*, **46**, 625–632 **(2005)**
11. Shojaei F., Wu X., Zhong C., Yu L., Liang X. H., Yao J., Blanchard D., Bais C., Peale F. V., Van Bruggen N., Ho C. Ross J., Tan M., Carano R. A., Meng Y. G. and Ferrara, N. Bv8 regulates myeloid-cell-dependent tumour angiogenesis, *Nature*, **450**, 825– 831 **(2007)**
12. Thompson W. J. and Melamed J. Y. Preparation of morpholinecarboxa-mides as prokineticin 2 receptor antagonists, Patent WO2007067511 **(2007)**