

## Microwave assisted synthesis of pyrimido[4,5-d]pyrimidine derivatives in dry media

A.H. Kategaonkar, S.A. Sadaphal, K.F. Shelke, B.B. Shingate, M.S. Shingare\*

*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University  
Aurangabad (M.S.) 431004, India*

**Summary.** Pyrimido[4,5-d]pyrimidine derivatives were synthesized by using an efficient, facile and solvent-free procedure. Here, a non-conventional synthetic procedure has been developed where solid support of alumina is used as energy transfer medium under microwave irradiation (MWI) which devoids hazards of solution phase reactions. The reaction time has been brought down from minutes to seconds with improved yield as compared to reported method.

**Keywords:** solvent-free, alumina, barbituric acid, pyrimido[4,5-d]pyrimidines, microwave irradiation.

**Introduction.** Combinatorial chemistry is playing an increasingly important role as one of the tool of modern medicinal chemistry for the rapid discovery of new leads [1]. The preparation of libraries of small organic molecules is a rapidly evolving area of research [2]. Pyrimido pyrimidines are annelated uracils that have attracted considerable interest in recent years. Derivatives of pyrimido pyrimidine are known to display a wide range of pharmacological activities, and their potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor [3], 5-phosphoribosyl-1-pyrophosphate synthetase [4] and dihydrofolate reductase [5] have been fully demonstrated. Numerous reports delineate the antitumour [6], antiviral [7], antioxidant [8], antifungal and heptatoprotective activities.

Multi-component reactions (MCRs) [9] are masterpieces of synthetic efficiency and reaction design. Therefore, mastering unusual combinations and sequences of elementary organic reactions under similar conditions is the major

conceptual challenge in engineering novel types of MCR. Most advantageously and practically, MCR can often be extended into combinatorial [10] and solid phase syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule based materials. Inevitably, many classical heterocyclic syntheses are MCR that are based upon carbonyl group condensations. Hence, medicinal chemistry is largely found on these easily accessible heterocyclic frameworks. The use of multicomponent reactions (MCRs) to generate interesting and novel, drug-like scaffolds is replete in the recent chemical literature [11]. For novel Biginelli-like scaffold synthesis, the use of the common open chain  $\beta$ -dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic  $\beta$ -diketones [12],  $\beta$ -ketolactones [13], cyclic  $\beta$ -diesters or  $\beta$ -diamides, benzocyclic ketones and  $\alpha$ -keto acids. All of these reactions were performed using conventional heating and reaction times were long.

Microwave promoted solvent-free reactions [14] are well known as environmentally benign methods that also usually provide improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity [15].

\*Corresponding author.

Tel.: +910240-2403311, fax: +91240-2400491

E-mail address: prof\_msshingare@rediffmail.com

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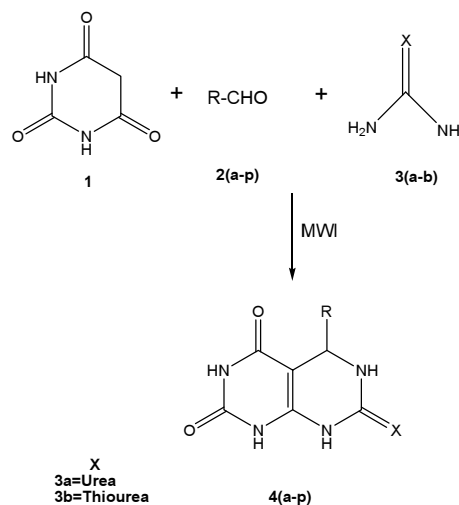
However, these procedures are practically limited as the solvents in microwave oven at elevated temperatures create high pressures, which may cause explosion. To circumvent these problems, there is a need for the development of newer methods which proceed under mild and solvent free condition. Solvents are often used to pre-absorb the substrates on to, and wash the products off the solid support. Benefits from using solvent-free approaches include improved safety by avoiding low-boiling solvents that would otherwise cause undesirable pressure increases during heating. For the transition of microwaves to the reactants, the solid support is the best option. Moreover they also provide an opportunity to work with open vessels and an enhanced possibility of upscaling the reactions on a preparative scale [16].

Nowadays solvent-free synthesized reactions much importance because of the absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for organic synthesis. Earlier reported procedures for the synthesis of pyrimido[4,5-d]pyrimidines typically involved longer reaction time and less yield [17]. In the present communication, we would like to describe the advantages of dry reaction techniques coupled with microwave activation and their applications to organic synthesis using solid supports [18].

**Result and discussion.** In view of the above mentioned limitations of the reported method, pharmacological importance of heterocycles and our ongoing endeavors to conduct organic synthesis under solvent free conditions [19], we describe a expeditious solventless microwave accelerated approach for the rapid assembly of pyrimido[4,5-d]pyrimidines. Aromatic aldehydes (**2a-m**, 0.01 mmol) on reaction with barbituric acid (**1**, 0.01 mmol) and urea/thiourea (**3a-b**, 0.01mmol) using dry conditions yielded corresponding pyrimido[4,5-d]pyrimidines (Scheme 1).

As far as our interest in investigating the facile, rapid and expeditious solventless methodology for pyrimido[4,5-d]pyrimidine, we tried the reaction of benzaldehyde (**2a**, 0.01 mmol), with barbituric acid (**1**, 0.01 mmol) and urea (**3a**, 0.01 mmol) with two different approaches to observe the effect of solid support. We carried

Scheme 1  
Synthesis of pyrimido[4,5-d]pyrimidine derivatives using alumina under solvent-free condition



out the reaction in absence of neutral alumina and in presence of neutral alumina. Here we observe the considerable changes as reaction rate enhancement occurred by bringing down the reaction time from minutes to seconds with improved yield as compared to reported method. The optimization was done by varying microwave power from 150 watts to 600 watts.

All results during this optimization were summarized in Table 1. Firstly, we observe without neutral alumina yield was very poor when power was 150 and 300 watts (Table 1, 10-15 %) and above 600 watts there is no appreciable change in yield (Table 1, 30-50 %) With neutral alumina it was observed that by increase in power up to 600 watts, there was increase in yield and shortened reaction time with solid support of neutral alumina. Beyond the 600 watts there was no significant change in reaction time and yield.

Thus a microwave power 600 watts was cho-

Table 1  
Optimization of time for benzaldehyde

| Entry | Power (watts) | Time     | Yield (%) <sup>a</sup>              |  |
|-------|---------------|----------|-------------------------------------|--|
|       |               |          | With Al <sub>2</sub> O <sub>3</sub> | Without Al <sub>2</sub> O <sub>3</sub> |
| 1     | 150           | 7 min    | 50                                  | 10                                     |
| 2     | 300           | 4.50 min | 60                                  | 15                                     |
| 3     | 450           | 3 min    | 75                                  | 30                                     |
| 4     | 600           | 30 sec   | 95                                  | 35                                     |
| 5     | 750           | 30 sec   | 95                                  | 50                                     |

<sup>a</sup>Isolated Yields.

Microwave assisted solvent-free solid neutral alumina supported synthesis of pyrimido[4,5-d]pyrimidine derivatives (power=600 watts)

| Entry | R  | X | Time         |                 | Yield(%) <sup>b</sup> |          | M. P.(°C)            |          |
|-------|--|---|--------------|-----------------|-----------------------|----------|----------------------|----------|
|       |  |   | Found (sec.) | Reported (min.) | Found                 | Reported | Found                | Reported |
| 4a    | C <sub>6</sub> H <sub>5</sub>                                    | O | 30           | 2.3             | 95                    | 87       | 247-250              | 244-246  |
| 4b    | 2-OH C <sub>6</sub> H <sub>4</sub>                               | O | 35           | 3.3             | 96                    | 82       | 218-220              | 220-222  |
| 4c    | 4-Cl C <sub>6</sub> H <sub>4</sub>                               | O | 30           | 3.0             | 96                    | 86       | 294-295              | 296-298  |
| 4d    | 4-OMe C <sub>6</sub> H <sub>4</sub>                              | O | 35           | 2.0             | 97                    | 85       | 285-287              | 284-286  |
| 4e    | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>                  | O | 35           | –               | 96                    | –        | 248-250 <sup>c</sup> | –        |
| 4f    | 4- OH C <sub>6</sub> H <sub>4</sub>                              | O | 35           | –               | 87                    | –        | 210-212 <sup>c</sup> | –        |
| 4g    | 4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | O | 35           | –               | 88                    | –        | 255-257 <sup>c</sup> | –        |
| 4h    | 4-OH, 3-OMe C <sub>6</sub> H <sub>4</sub>                        | O | 25           | –               | 85                    | –        | 275-277 <sup>c</sup> | –        |
| 4i    | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>                  | O | 30           | –               | 70                    | –        | 202-204 <sup>c</sup> | –        |
| 4j    | 4-Br C <sub>6</sub> H <sub>4</sub>                               | O | 30           | –               | 87                    | –        | 210-212 <sup>c</sup> | –        |
| 4k    | 2-Cl-3-Quinolonyl  | O | 40           | 3.3             | 95                    | 87       | 282-284              | 280      |
| 4l    | Piperonyl  | O | 40           | 2.0             | 94                    | 85       | 294(d)               | >300(d)  |
| 4m    | C <sub>6</sub> H <sub>5</sub>                                    | S | 30           | 2.3             | 95                    | 90       | 294-295              | 290-292  |
| 4n    | 2-OH C <sub>6</sub> H <sub>4</sub>                               | S | 35           | 3.0             | 94                    | 80       | 198-200              | 200-202  |
| 4o    | 4-Cl C <sub>6</sub> H <sub>4</sub>                               | S | 25           | 3.0             | 98                    | 92       | 280(d)               | 278(d)   |
| 4p    | 4-OMe C <sub>6</sub> H <sub>4</sub>                              | S | 40           | 2.3             | 96                    | 88       | >300(d)              | >300     |

Reported data [17] <sup>b</sup> Isolated yields based upon starting aldehyde. <sup>c</sup> Newly synthesized compounds.

sen as the optimal one with solid support of neutral alumina under MWI. Under these optimized reaction conditions the expected pyrimido[4,5-d]pyrimidine (Table 2, entry 4a) was obtained with 95 % yield within 30 seconds. Hence all the derivatives of pyrimido[4,5-d]pyrimidines were prepared by microwave power 600 watts with neutral alumina (Table 2).

**Typical experimental procedure.** A mixture of barbituric acid (0.01 mmol), an aromatic aldehyde (0.01 mmol), urea or thiourea (0.01 mmol) and 1 gm of neutral alumina (Al<sub>2</sub>O<sub>3</sub>) irradiated in a microwave oven operating medium power (600 watts) for appropriate time (Table 2). Progress of reaction was monitored by thin layer chromatography using ethyl acetate: hexane (2:8) solvent system.

After completion of reaction, the reaction mixture was cooled to room temperature and poured on crushed ice. Recrystallization was done in dimethyl formamide and the neutral alumina is recovered by simple filtration. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by thin layer chromatography (TLC) on Merck silica gel plates. IR spectra were recorded on a matrix of KBr with Perkin-Elmer 1430 spectrometer. <sup>1</sup>H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (400 MHz), Mass spectra [ES-MS] were recorded on a Water-Micro

mass Quattro-II spectrophotometer. For the microwave irradiation experiments described below, a microwave oven equipped with a turntable was used (LG Smart Chef MS-255R operating at 2450 MHz having maximum output of 900 W) for reaction.

**5,6-dihydro-5-p-tolylpyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4e).** IR (KBr, cm<sup>-1</sup>): 3490, 3250, 3125, 2867, 1697, 1616, 1468. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ ppm): 10.93 (s, 2H, NH), 10.03 (s, 1H, NH), 7.94 (s, 1H, NH), 6.97-6.86 (m, 4H, H<sub>arom</sub>), 5.89 (s, 1H, 5-H), 2.88 (s, 3H, CH<sub>3</sub>). Mass (ES/MS): m/z 273 [M+H]<sup>+</sup>.

**5,6-dihydro-5-(4-hydroxyphenyl)pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4f).** IR (KBr, cm<sup>-1</sup>): 3478, 3265, 3193, 3118, 1711, 1608, 1526. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ ppm): 11.30 (s, 1H, NH), 11.02 (s, 2H, NH), 8.40 (s, 1H, NH), 7.1-7.14 (m, 4H, H<sub>arom</sub>), 4.9 (s, 5-H). Mass (ES/MS): m/z 275 [M+H]<sup>+</sup>.

**5-(4-(dimethylamino)phenyl)-5,6-dihydro-pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4g).** IR (KBr, cm<sup>-1</sup>): 3181, 3041, 2842, 1650, 1520. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ ppm): 11.20 (s, 1H, NH), 10.98 (s, 2H, NH), 8.20 (s, 1H, NH), 6.6-6.8 (m, 4H, H<sub>arom</sub>), 5.58 (s, 1H, 5-H), 2.89 (s, 6H, CH<sub>3</sub>). Mass(ES/MS): m/z 302 [M+H]<sup>+</sup>.

**5,6-dihydro-5-(4-hydroxy-3-methoxyphenyl)pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4h).** IR (KBR, cm<sup>-1</sup>): 3279, 3070, 2866, 1667, 1501. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ

ppm): 11.25 (s, 2H, NH), 10.80 (s, 1H, NH), 8.45 (s, 1H, NH), 6.80-7.20 (m, 4H, H<sub>arom</sub>), 5.89 (s, 1H, 5-H), 3.40 (s, 3H, OCH<sub>3</sub>). Mass (ES/MS): m/z 305 [M+H]<sup>+</sup>.

**5,6-dihydro-5-(4-nitrophenyl)pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4i).** IR (KBR, cm<sup>-1</sup>): 3382, 3191, 3087, 2965, 2856, 1650, 1515. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ ppm): 11.40 (s, 1H, NH), 11.20 (s, 2H, NH), 10.18 (s, 1H, NH), 8.20-8.40 (m, 4H, H<sub>arom</sub>), 5.46 (s, 1H, 5-H). Mass (ES/MS): m/z 304 [M+H]<sup>+</sup>.

**5-(4-bromophenyl)-5,6-dihdropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4j).** IR (KBR, cm<sup>-1</sup>): 3200, 3044, 2837, 1620, 548. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz, δ ppm): 11.30 (s, 2H, NH), 10.01 (s, 1H, NH), 8.6 (s, 1H, NH), 7.20-

7.43 (m, 4H, H<sub>arom</sub>), 5.59 (s, 1H, 5-H). Mass (ES/MS): m/z 336 [M+H]<sup>+</sup>.

**Conclusion.** We have described an improved, efficient and one pot synthesis of pyrimido[4,5-d]pyrimidine derivatives via a three-component cycloaddition reaction. Another advantage of this method is excellent yields in shorter reaction time with high purity of the products.

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#### Синтез похідних піримідо[4,5-d]піримідинів у сухому середовищі за допомогою мікрохвильового випромінювання

А.Х. Катгаонкар, С.А. Садапхал, К.Ф. Шелке, Б.Б. Шингате, М.С. Шингаре

Університет ім. Доктора Бабасахеба Амбедкара Марасвади  
м. Аурангабад, Індія

**Резюме.** Похідні піримідо[4,5-d]піримідину синтезовано за допомогою простого й ефективного методу без застосування розчинника. Розроблено нетрадиційний спосіб синтезу, за якого нерухому підкладку із оксиду алюмінію використано як середовище для передачі енергії при мікрохвильовому випромінюванні, що запобігає негативним ефектам, які обумовлюють реакції у фазі розчинника. Новий метод дає змогу скоротити час реакції від декількох хвилин до кількох секунд і покращити її вихід.

**Ключові слова:** метод без використання розчинника, оксид алюмінію, барбітурова кислота, піримідо[4,5-d]піримідин, мікрохвильове випромінювання.

#### References

- (a) *Gordan E.M., Barrett R.W., Dower W.J., Fodor S.P.A., Gallop M.A.* Applications of combinatorial technologies to drug discovery. 2. combinatorial organic synthesis, library screening strategies, and future directions // *J. Med. Chem.* — 1994. — 37. — P. 1385-1401. (b) *Virgilio A.A., Ellman J.A.* Simultaneous solid-phase synthesis of β-turn mimetics incorporating side-chain functionality // *J. Am. Chem. Soc.* — 1994. — 116. — P. 11580-11581. (c) *Freier S.M., Konings D.A.M., Wyatt J.R., Ecker D.J.* Deconvolution of combinatorial libraries for drug discovery: a model system // *J. Med. Chem.* — 1995. — 38. — P. 344-352. (d) *Gordeev M.F., Gordon E.M., Patel D.V.* Solid-phase synthesis of β-Sultams // *J. Org. Chem.* — 1997. — 62. — P. 8177-8181.
- (a) *Bunin B.A., Ellman J.A.* A general and expedient method for the solid-phase synthesis of 1,4-benzodiazepine derivatives // *J. Am. Chem. Soc.* — 1992. — 114. — P. 10997-10998. (b) *Yu K.-L., Deshpande M.S., Vyas D.M.* // *Tetrahedron Lett.* — 1994. — 35. — P. 8919-8922. (c) *Smith P.W., Q Lai J.Y.Y., Whittington A.R., Cox B., Houston J.G., Stylli C.H., Banks M.N., Tiller P.R.* Synthesis and biological evaluation of a library containing potentially 1600 amides/esters. A strategy for rapid compound generation and screening // *Bioorg. Med. Chem. Lett.* — 1994. — 4. — P. 2821-2824. (d) *Kick E. K., Ellman J.A.* Expedient method for the solid-phase synthesis of aspartic acid protease inhibitors directed toward the generation of libraries // *J. Med. Chem.* — 1995. — 38. — P. 1427-1436. (e) *Holmes C.P., Jones D.G.* Reagents for combinatorial organic synthesis: development of a new o-nitrobenzyl photolabile linker for solid phase synthesis // *J. Org. Chem.* — 1995. — 60. — P. 2318-2319. (f) *Campbell D.A., Bermak J.C., Burkoth T.S., Patel D.V.* A transition state analog inhibitor combinatorial library // *J. Am. Chem. Soc.* — 1995. — 117. — P. 5381-5382.
- Rewcastle G.W., Bridges A.J., Fry D.W., Rubin J.R., Denny W.A.* Tyrosine kinase inhibitors. 12. Synthesis and structure-activity relationships for 6-substituted 4-(phenylamino) pyrimido [5,4-d] pyrimidines designed as inhibitors of the epidermal growth factor receptor // *J. Med. Chem.* — 1997. — 40. — P. 1820-1826.
- Fry D.W., Becker M.A., Switzer R.L.* Inhibition of human 5-phosphoribosyl-1-pyrophosphate synthetase by 4-amino-8-(beta-d-ribofuranosylamino)-pyrimido[5,4-d]pyrimidine-5'-monophosphate: evidence for interaction at the ADP allosteric site // *Mol. Pharmacol.* — 1995. — 47. — P. 810-815.
- Gready J.E., McKinlay C., Gebauer M.G.* Synthesis of quaternised 2-aminopyrimido[4,5-d]pyrimidin-4(3H)-ones and their biological activity with dihydrofolate reductase // *Eur. J. Med. Chem.* — 2003. — 38. — P. 719-728.

6. Sanghvi Y.S., Larson S.B., Matsumoto S.S., Nord L.D., Smee D.F., Willis R.C., Avery T.H., Robins R.K., Revankar G.R. Antitumor and antiviral activity of synthetic  $\alpha$ - and  $\beta$ -ribonucleosides of certain substituted pyrimido[5,4-d]pyrimidines: a new synthetic strategy for exocyclic aminonucleosides // *J. Med. Chem.* — 1989. — 32. — P. 629-637.
7. Tenser R.B., Gaydos A., Hay K.A. Inhibition of herpes simplex virus reactivation by dipyrindamole // *Antimicrob. Agents Chemother.* — 2001. — 45. — P. 3657-3659.
8. De la Cruz J.P., Carrasco T., Ortega G., Sanchez De la Cuesta F. Inhibition of ferrous-induced lipid peroxidation by pyrimido-pyrimidine derivatives in human liver membranes // *Lipids.* — 1992. — 27. — P. 192-194.
9. (a) Zhu J., Bienayme H. Multicomponent Reactions // Wiley-VCH, Weinheim — 2005. (b) Domling A. Recent developments in Isocyanide based multicomponent reactions in applied chemistry // *Chem. Rev.* — 2006. — 17. — P. 106. (c) Ram V.J., Goel A., Sarkhel S., Maulik P.R. A convenient synthesis and hepatoprotective activity of Imidazo[1,2-c]pyrimido[5,4-e]pyrimidine, tetraazaacenaphthene and tetraazaphenalene from cyclic ketene amins through tandem addition-cyclization reactions // *Bioorg. Med. Chem.* — 2002. — 10. — P. 1275-1280.
10. Domling A. Isocyanide based multicomponent reactions in combinatorial chemistry // *Combinatorial Chemistry & High Throughput Screening.* — 1998. — 1. — P. 1-22.
11. (a) Ugi I., Domling A., Gruber B., Almstetter M. Multicomponent reactions and their libraries — a new approach to preparative organic chemistry // *Croatia Chem. Acta.* — 1997. — 70. — P. 631-647. (b) Armstrong R., Combs A., Tempest P., Brown D. Keating T. Multiple-component condensation strategies for combinatorial library synthesis // *Acct. Chem. Res.* — 1996. — 29. — P. 123-131.
12. Yarim M., Sarac S., Kilic F.S., Erol K.I. Synthesis and in vitro calcium antagonist activity of 4-aryl-7,7-dimethyl-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives // *Farmaco.* — 2003. — 58. — P. 17-24.
13. Byk G., Gettlieb H.E., Herscovici J., Mirkin F.J. New regioselective multicomponent reaction: one pot synthesis of spiro heterobicyclic aliphatic rings // *Comb. Chem.* — 2000. — 2. — P. 732-735.
14. Shaabani A., Bazgir A. Microwave-assisted efficient synthesis of spiro-fused heterocycles under solvent-free conditions // *Tetrahedron Lett.* — 2004. — 45. — P. 2575-2577.
15. (a) Abelman M.M., Smith S.C., James D.R. Cyclic ketones and substituted  $\alpha$ -keto acids as alternative substrates for novel Biginelli-like scaffold syntheses // *Tetrahedron Lett.* — 2003. — 44. — P. 4559-4562. (b) Atonio de la Hoz; Ángel Díaz-Ortiz, Andrés Moreno. Microwaves in organic synthesis. Thermal and non-thermal microwave effects // *Chemical Society Reviews.* — 2005. — 34. — P. 164-178. (c) Lidstrom P., Tierney J., Wathey B., Westman J. Microwave assisted organic synthesis—a review // *Tetrahedron.* — 2001. — 57. — P. 9225-9283.
16. Loupy A., Pigeon P., Ramdani M. Jacquault P. Solid-liquid phase transfer catalysis without solvent coupled with microwave irradiation: A quick and efficient method for saponification of esters // *Synth. Commun.* — 1994. — 24. — P. 159-165.
17. Kidwai M., Singhal K., Kukreja S. One-pot green synthesis for pyrimido[4,5-d]pyrimidine derivatives // *Z. Naturforsch.* — 2007. — 62. — P. 732-736.
18. Kidwai M. Dry media reactions // *Pure Appl. Chem.* — 2001. — 73. — P. 147-151.
19. (a) Sadaphal S.A., Shelke K.F., Sonar S.S., Shingare M.S. Ionic promoted solvent free synthesis of bis(indolyl) methanes // *Central Euro. J. Chemistry.* — 2008. — 6. — P. 622-626. (b) Karale B.K., Chavan V.P., Mane A.S., Hangarge R.V., Gill C.H., Shingare M.S. Microwave induced synthesis of 3-methyl-4-[(chroman-3-yl) methylene]-1-phenyl pyrazolin-5-(4H)-ones with alumina support in solvent free conditions // *Synthetic Comm.* — 2002. — 32. — P. 497-503. (c) Gajare A.S., Sabade D.P., Shingare M.S., Wakharkar R.D. Microwave accelerated tetrahydropyranylation and dehydropyranylation of alcohols, phenols and thiols catalyzed by hydrated zirconia // *Synthetic Commu.* — 2002. — 32. — P. 1549-1555. (d) Madje B.R., Shindalkar S.S., Ware M.N. Shingare M.S. Zinc mediated solvent-free synthesis of 3,4-dihydro pyrimidin-2(1H)-ones under microwave irradiation // *Chemistry: An Indian Journal.* — 2005. — 2. — P. 95-98. (e) Shindalkar S.S., Madje B.R., Shingare M.S. Microwave induced protection and deprotection of 4-oxo-(4H)-1-benzopyran-3-carbaldehydes catalyzed by Enviocat EPZ10<sup>®</sup> // *Mendeleev Commun.* — 2007. — 17. — P. 43-44.