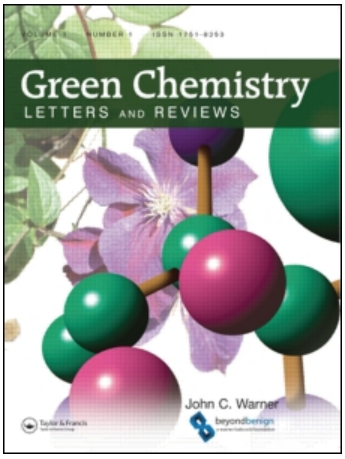

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Novel pyrimidine derivatives by sonication and traditional thermal methods

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RESEARCH REVIEW

Novel pyrimidine derivatives by sonication and traditional thermal methods

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A series of bis-compounds **(2)** were synthesized by condensing dihydro-1,3-(disubstituted)phenyl-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione with hippuric acid in presence of acetic anhydride. The compound **(2)** on further treatment with aromatic amine afforded dihydropyrimidine **(3)** through an eco-friendly procedure by sonication. The sonication method reduces time and gives higher yields, and also the effluent produced is free from hazardous contamination and organic by-products. The novel pyrimidines were also synthesized by traditional methods for comparison purposes and sonication method was found to be superior. Structures of the synthesized compounds have been elucidated on the basis of elemental analysis and spectral data.

Keywords: thiobartiturates; hippuric acid; conventional method; sonication method

Introduction

Heterocyclic compounds, both naturally occurring and synthetically produced, exhibit various pharmacological and biological properties and are, therefore, interesting synthetic targets in the search of therapeutic agents. Small heterocyclic molecules are especially considered ''privileged'' structures for the synthesis and development of new drugs. Derivatives of imidazole, pyrimidines, and isoxazole have played crucial roles in the history of heterocyclic chemistry and have been used extensively as important pharmacophores and synthons in the field of organic chemistry and drug design. Owing to their versatile chemotherapeutic importance, a significant amount of research has been focused on these nuclei. Imidazole derivatives have attracted considerable attention in recent years as these are endowed with a wide range of pharmaceutical activities like antifungal (*1*), antihypertensive (*2*), antioxidant (*3*), cardiotonic (*4*), antithrombotic (*5*), HIV-IPR inhibitors (*6*), IL-1 inhibitor (*7*), anti-cionvulsant (*8*), and anti-hepatitis B and C virus activity (*9*). Pyrimidine derivatives serve both as biomimetic and reactive pharmacophores due to their diverse medicinal properties, such as antitumor (*10*), anticancer (lungs, breasts, and CNS cancer) (*11*), immunodelator (*12*), antifoliate (*13*), antiviral (*14*), tyrosine kinase inhibitors (*15*), COX-2 inhibitors (*16*), antihypertensive (*17*), and also active against Y181C HIV-1 mutant strain (*18*). Similarly, isoxazoles are widely investigated for therapeutic uses, such as antiepileptic (*19*), PPAR-δ agonists (*20*), acetyl coline-esterase inhibitors (*21*), anti-inflammatory (*22*), acrosine inhibitors, and anti-fungal activity (*23*). The design of safe synthetic methods has given important position to ultrasound irradiation techniques as a new source of energy for organic reactions. Ultrasound enhances some processes through a physical phenomenon called cavitation, the formation, growth, and collapse of bubbles in an elastic liquid. These bubbles create local high pressure and temperature that leads to high energy radical mechanisms with some physical effects, such as micromixing, mass transport, or reduction of particles size (*24*). The advantages of ultrasound-assisted chemical reactions include higher yields, shorter reaction times, and milder reaction conditions when compared with traditional synthetic methods (*25–27*). The use of ultrasound irradiation techniques for activating various reactions is well documented in the literature (*28–35*).

Our research group has a longstanding interest in the synthesis of heterocyclic compounds by newer methods, such as microwave (*36–39*) and sonication (*40–42*), aiming at the development of more rapid and advantageous construction of libraries of small heterocyclic compounds. As a result, we have recently reported the ultrasound accelerated synthesis of bis-benzothiazepine and bis-thiophine compounds and their biological evalution (*40*), the synthesis and biological studies of bis (triazole/thiadiazole) by sonication (*41*), and the ultrasound-mediated synthesis of biological active bis-spiro compounds (*42*). Led by the

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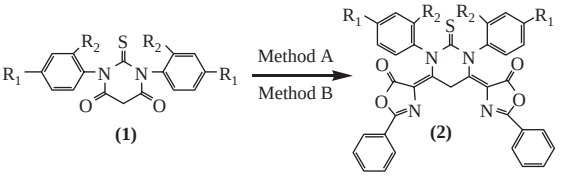
above, herein we report the eco-friendly synthesis of novel pyrimidine derivatives containing imidazole and oxazole moieties which have diverse pharmacological properties. The condensation of dihydro-1,3-(disubstituted)phenyl-2-thioxopyrimidine-4,6(1*H*, 5*H*)-dione (*43*) (**1**) with hippuric acid in the presence of acetic anhydride and sodium acetate resulted in the formation of 4,6-bis-[2′-phenyl-1′,3′-oxazol-5′-one]-1,3-(disubstituted)phenyl-2-thioxo-5-dihydropyrimidine (**2a–c**) (Scheme 1). Various aromatic amines were then reacted with compound **(2)** to give the corresponding 4,6-bis-[1-(substituted)phenyl-2-phenyl-imidazol-5-one]-1,3-(disubstituted)phenyl-2-thioxo-5-dihydropyrimidines (**3a–h**) (Scheme 2). Keeping in view of the advantages of ultrasound irradiation techniques, the reaction was also carried out under sonication conditions. The formation of compounds (**3**) was completed in 35 min under sonication conditions, compared to the conventional method, which required 6 h. The compounds obtained by both the routes were found to be identical as they showed the same melting point and similar spectral data. The comparative studies, elemental analysis together with spectral data, revealed that the compounds were successfully synthesized and are summarized in Table 1.

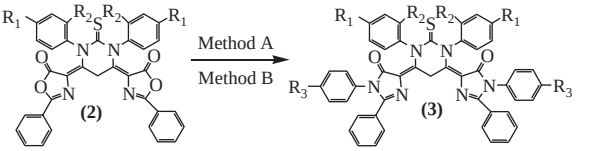
Experimental

The chemicals were supplied by E. Merck (Germany) and S.D Fine Chemicals (India). The melting points of synthesized compounds were determined in open capillary tubes using a Veego VMP-1 melting point apparatus, expressed in degrees Celsius and are uncorrected. The purity of the compounds was monitored by thin layer chromatography (TLC) on silica gel-coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra (cm^{-1}; potassium bromide disc) were recorded on a Perkin–Elmer spectrophotometer in the range of 4000–400 cm^{-1}. ^1H NMR spectra were recorded on a Brucker Avance 300 MHz NMR spectrophotometer from International Equipment Trading Ltd., using $CDCl_3$ as solvent and TMS as an internal



Method A = Conventional method, time 2 h
Method B = Sonication method, time 25 min

Scheme 1. Synthesis of bis-compounds **(2)**.



Method A = Conventional method, time 6 h
Method B = Sonication method, time 35 min

Scheme 2. Preparation of dihydropyrimidine **(3)**.

standard (chemical shifts in (δ), given in ppm). C, H, and N estimation were carried out on Carlo Erba 1108 (CHN) Elemental Analyser. Experiments under ultrasound irradiation were carried out using a probe sonicator manufactured by Dakshin.

General procedure for synthesis for bis-pyrimidine (compound 2)

4,6-Bis-[2′-phenyl-1′,3′-oxazol-5′-one]-1,3-(disubstituted)phenyl-2-thioxo-5-dihydropyrimidine

Conventional method A

A mixture of dihydro-1,3-(disubstituted)phenyl-2-thioxopyrimidine-4,6 (1*H*,5*H*)-dione (0.03 mol), hippuric acid (10.75 g, 0.06 mol), acetic anhydride (20 mL), and anhydrous sodium acetate (0.49 g, 0.006 mol) was stirred mechanically and refluxed on a water bath for 2 h. After completion of the reaction (TLC), a bright colored crystal separated out was filtered off and washed successively with cold water. The collected crystals were recrystallized from ethanol to obtain compound (**2a–c**).

Sonication method B

A mixture of 1,3-(disubstituted)phenyl-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (0.03 mol), hippuric acid (10.75 g, 0.06 mol), acetic anhydride (20 mL), and anhydrous sodium acetate (0.49 g, 0.006 mol) was stirred mechanically and was exposed to ultrasound irradiation for 25 min. Upon completion of the reaction (monitoring on TLC), the mixture was poured over crushed ice. The product precipitated out was filtered, washed with water, and recrystallized from ethanol to obtain compound (**2a–c**).

2(a) IR (KBr, ν_{max} cm^{-1}): 1676 (C=O), 1593 (C=N), 1490 (C=C), 747 (C=S); ^1H NMR (300 MHz $CDCl_3$): δ 2.73 (s, 2H, CH_2), 7.21–8.10 (m, 20H, ArH). ^{13}C NMR (75 MHz $CDCl_3$): δ 26.23, 105.2, 124.8, 126.5, 129.1, 134.2, 146.32, 166.65, 177.8; MS (*m*/*z*): 582 (M^+). [Found: C, 70.08; H, 3.77; N, 9.59; $C_{34}H_{22}N_4O_4S$ requires: C, 70.10; H, 3.78; N, 9.62%].

Table 1. Physical and analytical data of compounds (**2**) and (**3**).

Compounds	R_1	R_2	R_3	Yield, % Conv	Yield, % Soni	Melting point
2a	H	H	H	58	69	162
2b	CH_3	H	H	56	74	78
2c	H	Cl	H	57	72	118
3a	H	H	H	62	79	218
3b	H	H	CH_3	61	80	202
3c	H	H	OCH_3	57	81	210
3d	H	H	Cl	58	78	212
3e	H	Cl	H	65	80	162
3f	H	Cl	CH_3	61	81	174
3g	H	Cl	OCH_3	64	82	158
3h	H	Cl	Cl	67	80	147

Note: Conv, conventional method; Soni, sonication method.

2(c) IR (KBr, ν_{max} cm^{-1}): 1680 (C=O), 1571 (C=N), 1491 (C=C), 723 (C=S), 693.7 (C–Cl); ^{1}H NMR (300 MHz $CDCl_3$): δ 2.71 (s, 2H, CH_2), 6.81–8.78 (m, 18H, ArH). ^{13}C NMR (75 MHz $CDCl_3$): δ 22.21, 27.12, 104.21, 126.4, 129.4, 131.23, 134.4, 144.43, 165.45, 176.45 MS (*m*/*z*): 650 (M^+). [Found: C, 62.74; H, 3.05; N, 8.58; $C_{34}H_{20}Cl_2N_4O_4S$ requires: C, 62.76; H, 3.07; N, 8.61%].

General procedure for synthesis for bis-pyrimidine (compound 3)

4,6-Bis-[1′-(substituted)phenyl-2′-phenylimidazol-5′-one]-1,3-(di-substituted)phenyl-2-thioxo-5-dihydropyrimidine

Conventional method A

A mixture of (**2**) (0.05 mol) and aromatic amines (0.005 mol) in anhydrous pyridine (50 mL) was heated under reflux on an oil bath for 6 h under anhydrous conditions. After completion of the reaction (TLC), the reaction mixture was poured into ice-cold water (100 mL) containing concentrated HCl (10 mL). A solid started to separate out, was allowed to settle for 1 h, was then filtered off and washed excessively with water, dried, and recrystallized from ethanol to give compound (**3a–h**).

Sonication method B

A mixture of (**2**) (0.05 mol) and aromatic amines (0.005 mol) in anhydrous pyridine (50 mL) was subjected to ultrasound irradiation for 35 min. After completion of the reaction, it was monitored by TLC and the mixture was poured into ice-cold water and washed with 1:1 HCl:water. The solid obtained was filtered off and recrystallized from ethanol to obtained compound (**3a–h**).

3(a) IR (KBr, ν_{max} cm^{-1}): 1668 (C=O), 1572 (C=N), 1495 (C=C), 738 (C=S); ^{1}H NMR (300 MHz $CDCl_3$): δ 2.57 (s, 2H, CH_2), 6.85–7.81 (m, 30H, ArH). ^{13}C NMR (75 MHz $CDCl_3$): δ 26.5, 103.23, 124.3, 126.5, 128.54, 129.23, 130.45, 134.34, 148.5, 169.43, 177.34; MS (*m*/*z*): 732 (M^+). [Found: C, 75.38; H, 4.35; N, 11.46; $C_{46}H_{32}N_6O_2S$ requires: C, 75.40; H, 4.37; N, 11.47%].

3(c) IR (KBr, ν_{max} cm^{-1}): 1662 (C=O), 1558 (C=N), 1488 (C=C), 735 (C=S); ^{1}H NMR (300 MHz $CDCl_3$): δ 2.57 (s, 2H, CH_2), 3.75 (s, 6H, $2 \times OCH_3$), 6.81–7.93 (m, 28H, ArH); MS (*m*/*z*): 760 (M^+). [Found: C, 72.70; H, 4.52; N, 10.58; $C_{48}H_{36}N_6O_4S$ requires: C, 72.72; H, 4.54; N, 10.60%].

3(f) IR (KBr, ν_{max} cm^{-1}): 1678 (C=O), 1534 (C=N), 1491 (C=C), 816 (C=S), 692 (C–Cl); ^{1}H NMR 300 MHz $CDCl_3$: δ 2.31 (s, 6H, $2 \times CH_3$), 2.67 (s, 2H, CH_2), 7.05–7.86 (m, 26H, ArH). ^{13}C NMR (75 MHz $CDCl_3$): δ 21.23, 26.23, 104.23, 121.23, 126.45, 127.23, 128.34, 130.32, 134.12, 136.65, 146.09, 164.76, 173.34; MS (*m*/*z*): 830 (M^+). [Found: C, 69.38; H, 4.07; N, 10.10; $C_{48}H_{34}Cl_2N_6O_2S$ requires: C, 69.39; H, 4.09; N, 10.12%].

3(g) IR (KBr, ν_{max} cm^{-1}): 1677 (C=O), 1579 (C=N), 1440 (C=C), 826 (C=S), 693 (C–Cl); ^{1}H NMR 300 MHz $CDCl_3$): δ 2.67 (s, 2H, CH_2), 3.73 (s, 6H, $2 \times OCH_3$), 6.77–7.84 (m, 26H, ArH). ^{13}C NMR (75 MHz $CDCl_3$): δ 25.89, 42.34, 103.65, 120.06, 124.78, 125.45, 126.12, 127.98, 130.11, 132.76, 135.02, 145.11, 163, 174.87; MS (*m*/*z*): 864 (M^+). [Found: C, 63.28; H, 3.19; N, 9.61; $C_{46}H_{28}Cl_2N_6O_2S$ requires: C, 63.30; H, 3.21; N, 9.63%].

Conclusion

We have demonstrated a simple and efficient procedure for the synthesis of pyrimidine derivatives using a sonication technique. The significant features of this

method include: (a) operation simplicity; (b) high yield of product; and (c) reduction of time.

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