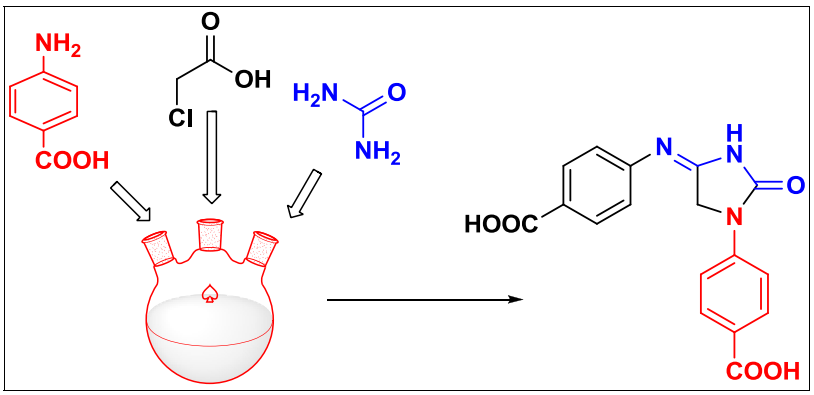
Conventional and Microwave-Activated the Synthesis of a Novel Series of Imidazoles, Pyrimidines, and Thiazoles Candidates

Yasser Selim[a]* and Mohamed H. M. Abd El-Azim[b]

[a]Faculty of Specific Education, Zagazig University, Zagazig 44519, Egypt
[b]Department of Chemistry, Faculty of Science, Zagazig University, Zagazig 44519, Egypt
*E-mail: y2selem@yahoo.com

Received January 15, 2018
DOI 10.1002/jhet.3176
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A novel series of imidazoles, pyrimidines, and thiazoles were synthesized using microwave irradiation and conventional method from commercial available *p*-aminobenzoic acid. Thus, one-pot condensation of *p*-aminobenzoic acid, urea, and chloroacetic acid have been provided two types of imidazole derivatives as separated mixture **2a** and **2b**. [3 + 2 + 1] Cyclocondensation of **2a**, benzaldehyde, and urea/thiourea in acidic medium afforded imidazolo oxazine derivative **3** and Imidazolothiazine **4**. Coupling of **2a** with benzene diazonium salt gave the phenyldiazenyl imidazolidine **5**. While the reaction of **2a**, thiourea, and benzaldehyde in sodium ethoxide afforded imidazolothiazine **6**. Oxidative cyclization of thiourea derivative **7** resulted a mixture of benzithiazole derivative **7a** and oxathiazole derivative **7b**. Cyclocondensation of **7a** with phenylenediamine and 4-methyl phenylenediamine furnished imidazole **8** and **9**, respectively. Reaction of *P*-aminobenzioc acid with potassium cyanate followed by Biginelli reaction with (acetyl acetone, ethyl acetoacetate, and diethyl malonate) and salicyladehyde in HCl tolerated pyrimidine derivatives **10a–c**, respectively. In the same manner, the reactions and short reaction time make microwave technique one of the greenest methodology for synthesis of this class of heterocyclic system.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. The imidazole nucleus is an important synthetic strategy in drug discovery [1] and plays an important role in areas such as natural products [2,3] and medicinal chemistry [2]. Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as sulfathiazole (antimicrobial drug), ritonavir (antiretroviral drug), abafungin (antifungal drug), and tiazofurin (antineoplastic drug) [4,5]. Recently, several protocols have already been described the synthesis of thiazoles and benzothiazoles derivatives [6–8]. Pyrimidines and its condensed derivatives are considered as privileged structures with a large spectrum of biological activities and considered as components of RNA and DNA. Several pyrimidine derivatives exhibit diverse pharmacological activities [9,10], as antimicrobial [11], analgesic [12], anti-inflammatory [13], and antitumor activity [14]. The new trend for the synthetic of compounds uses microwave irradiation (MWI) as a powerful technique for rapid and efficient synthesis [15–17]. The utility of MWI as alternative synthetic tool has advantages such as shorter reaction time, pure products, significant reaction yield, fewer side products, and greater selectivity [18–20]. In continuation of our previous studies on the development of new heterocyclic systems using simple and efficient procedures [21], we report here a facile and clean protocol for the synthesis of a new class of imidazoles, pyrimidines, and thiazoles using MWI as alternate energy source starting from readily available *p*-aminobenzoic acid.

RESULTS AND DISCUSSION

Three components cyclocondensation of *p*-aminobenzoic acid, urea, and chloroacetic acid using microwave irradiated for 5 min to provide two types of imidazole derivatives **2a** and **2b** in high yield (85% and 9%, respectively) (Table 1).

Table 1

Comparative data of conventional and microwave (MW) methods for the synthesis of compounds **2–10.**

Entry	Cpd no.	Conventional method (A) Time (h)	Yield (%)	MW method (min)	Yield (%)
1	**2a**	0.3	60	5	85
	2b		60		90
2	**3**	4	50	7	90
3	**4**	4	45	8	73
4	**5**	1	45	-	-
5	**6**	4	60	7	74
6	**7**	1	-	3	-
7	**7a**	0.5	55	3	70
	7b		40		65
8	**8**	6	35	10	75
9	**9**	6	30	12	68
10	**10**	1	-	3	-
11	**10a**	6	45	10	84
12	**10b**	6	35	12	85
13	**10c**	6	25	11	80

-, Time only.

The formation of **2b** may be resulted from the condensation of the second molecule of *p*-aminobenzoic acid with electrophilic carbonyl carbon of **2a** (Scheme 1). The infrared (IR) spectrum of imidazole derivative **2a** showed peaks at 3325, 3186, 1720, and 1651 cm^{-1} characteristic for OH, NH, and C=O. While ^1H NMR revealed signals at 12.71 and 9.31 ppm (exchange with D_2O) for carboxyl group and NH, respectively, in addition to, ArH's and CH_2 signals at 7.6–8.11 ppm and CH_2 signals at 4.67 ppm. ^{13}C NMR showed signals at 170.6, 169.0, and 168.1 ppm for three C=O group. While IR spectrum of **2b** revealed peaks at 3367 and 3186 cm^{-1} characteristic for OH and NH, respectively, and 1774, 1716, and 1678 cm^{-1} corresponding to three C=O groups.^1H NMR showed signals at 12.75 and 11.34 ppm (exchange with D_2O) for carboxyl group and NH, respectively.

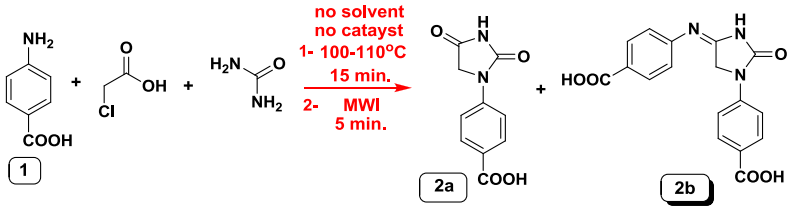
[3 + 2 + 1] Cyclocondensation of urea, imidazole derivative **2a**, and benzaldehyde under MWI for 7 min resulted oxazine cyclization forming imidazolo oxazine derivative **3** in high yield (90%) as shown in Table 1 and none of pyrimidine derivative **III** (Scheme 2), the conventional need 4 h of heating. Compound **3** characterized by OH, NH, and C=O absorption peaks at 3325, 1670, and 1654 cm^{-1}, respectively. IR spectrum also showed signals at 12.63 ppm (exchange with D_2O) for COOH proton and NH_2 at 9.21 ppm (exchange with D_2O). ^{13}C NMR showed signals at 167.5 and 152.4 ppm for two C=O group.

The formation of oxazine **3** *via* 1,4-addition of urea to 2a to give the intermediate II, followed by oxidation and subsequent [1,5] hydride shift under MWI for 8 min. The imidazolothiazine **4** was also obtained by addition of **2a**, thiourea, and benzaldehyde under reflux in acidic medium for 4 h (Scheme 3). Thiazine derivative **4** proved the presence of OH and NH at 3317 and two C=O at 1690 and 1654 cm^{-1}. While ^1H NMR (exchange with D_2O) signal was observed at 12.64 ppm for COOH proton and NH at 9.17 ppm (exchange with D_2O). Upon treatment of imidazole **2a** with phenyl diazonium, salt undergo coupling on (N) not (C) afforded azoimidazole **5** (Scheme 3). The structure of **5** potentiated by the presence of OH and absence of NH in IR spectrum which revealed two C=O groups at 1670 and 1654 cm^{-1}. Its ^1H NMR showed signal at 10.61 ppm (exchange with D_2O) for COOH proton in addition to Ar–H at 6.97–8.13 ppm and CH_2 protons at 4.69 ppm. ^{13}C NMR also detected three C=O signals at 169.2, 168.5, and 168.1 ppm.

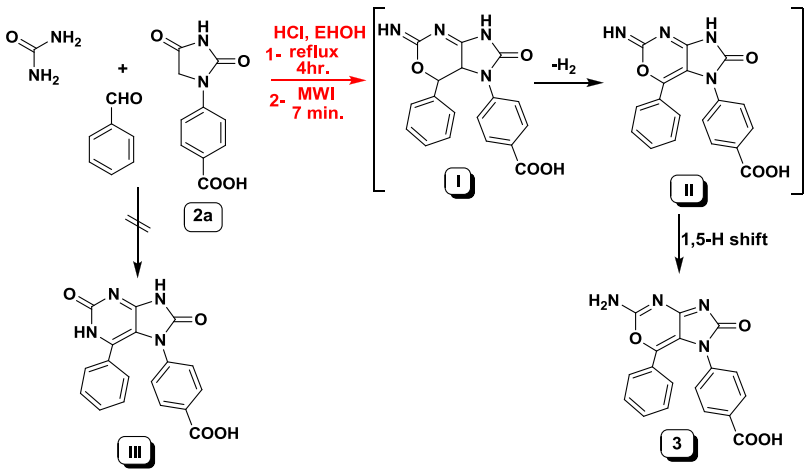
The imidazolothiazine **6** was obtained by heating of **2a**, thiourea, and benzaldehyde under MWI in basic medium for 7 min in 74% yield (Scheme 3, Table 1). IR spectrum of thiazine derivative **6** revealed the presence of bands at 3325, 3186, 1670, 1654, and 1589 cm^{-1} characterized for OH and NH. While ^1H NMR showed signal at 7.57–7.88 ppm for aromatic protons and signal at 9.17 ppm for two NH groups, in addition to, at 12.64 ppm for OH group which agreement with the structure.

Microwave irradiation assisted the oxidative cyclization of thiourea derivative **7** to benzothiazole and thiazole **7a,b** via the reaction with Br_2 in acidic medium for 3 min. The IR spectrum of benzithiazole derivative **7a** revealed OH, NH, and C=O stretching absorbing bands at 3174, 3132, and 1678 cm^{-1}, respectively. ^1H NMR revealed the presence of aromatic protons as multiplet at 7.57–8.17 ppm, signal at 8.86 ppm for NH, and signal at 13.03 ppm for COOH. ^{13}C NMR displayed signal at carbon at 167.5 and 166.7 ppm for two C=O and at 162.4 ppm for C=N. Oxathiazole derivative **7b** showed stretching absorbing

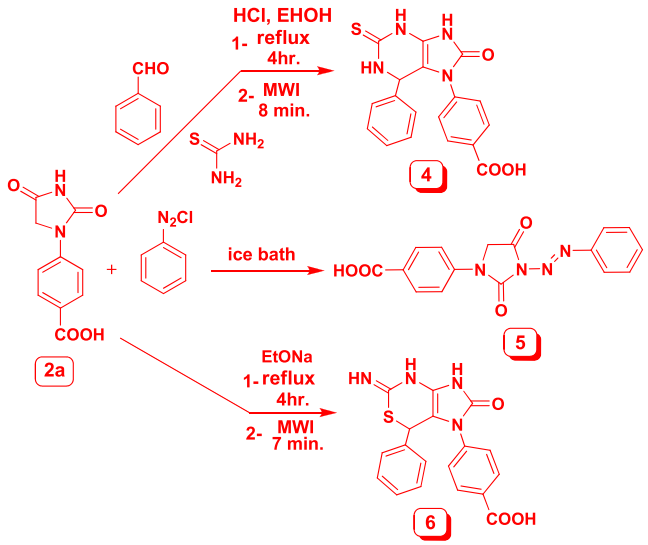
Scheme 1. One-pot synthesis of imidazoles **2a,b**. MWI, microwave irradiation. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. One-pot synthesis of imidazolo [4,5-*d*]oxazine **3**. MWI, microwave irradiation. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Synthetic routes of imidazoles **4**–**6**. MWI, microwave irradiation. [Color figure can be viewed at wileyonlinelibrary.com]

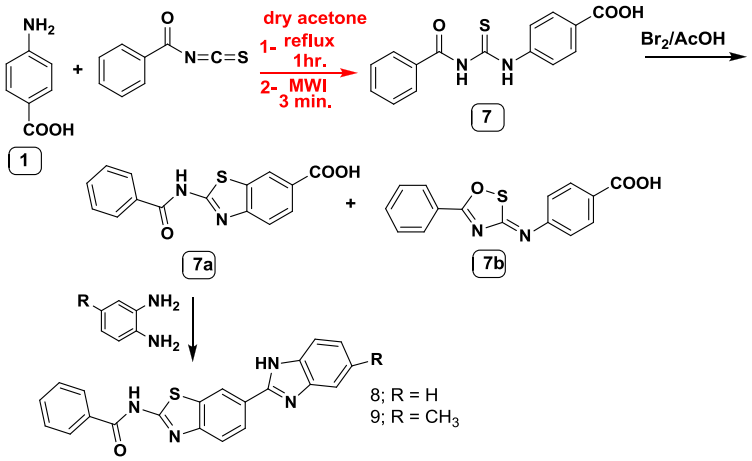


band at 1685 cm^{-1} for C═O group. The ^1H NMR provided signal at 12.81 ppm for COOH (exchange with D_2O), in addition to aromatic multiplet at 7.43–8.26 ppm.

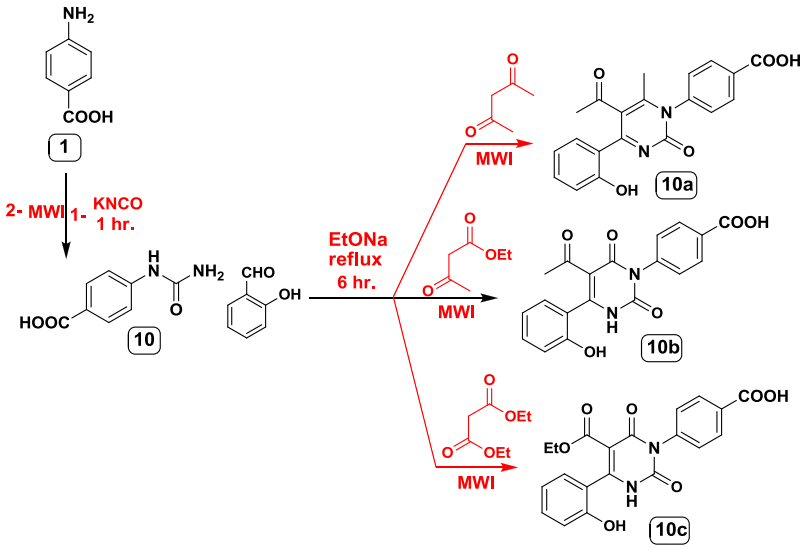
Cyclocondensation using MWI for compound **7a** and phenylenediamine, 4-methyl phenylenediamine afforded imidazole **8** and **9** for (Scheme 4) (Table 1). IR spectrum of **8** and **9** gave broad absorption bands at 3340 cm^{-1} due to stretching vibration of two NH of imidazole and anilide. The ^1H NMR spectra of **8** and **9** showed downfield protons for four NH at 12.25, 12.54, 12.18, and 12.21 ppm.

Treatment of *p*-aminobenzioc acid with potassium cyanate afforded the urea derivative **10**, which underwent one-pot Bignelli reaction in MW (Table 1) via the reaction with salicylaldehyde and active methylene dicarbonyl compounds (*viz*, acetyl acetone, ethyl acetoacetate, and diethyl malonate) in the presence of HCl for 10–12 min afforded pyrimidine derivatives **10a–c**, respectively (Scheme 5). The structures of pyrimidine derivatives 10a–c were confirmed by spectral data. Thus, IR spectra of the products **10a–c** showed bands at 1662, 1716, 1685, and 1708 cm^{-1} for ester and amide carbonyl groups. ^1H NMR data of pyrimidine **10a** showed four signals at 2.74, 2.89, 9.59, and 9.71 ppm for two CH_3 and two OH groups, in addition to aromatic signals between 6.77–7.52 ppm as multiplet. ^{13}C NMR spectrum of **10b** showed signals at 117.1, 126.3, 126.8, 127.0, 127.9, 128.7, 130.7, 132.1, 133.0, 138.0, 156.06, 163.2, 164.1, and 168.5 ppm characteristic for Ar─C and four C═O. ^1H NMR spectrum of **10c** showed signals at 1.3 and 4.33 ppm as triplet and quartet at 4.33 ppm for CH_3CH_2, signals at 7.89 and 10.05 ppm for two OH and signal at 8.61 ppm for NH (exchange with D_2O).

Scheme 4. Synthetic pathways of imidazoles **7**–**9**. MWI, microwave irradiation. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 5. Synthetic routes of pyrimidines **10a**–**c**. MWI, microwave irradiation. [Color figure can be viewed at wileyonlinelibrary.com]



CONCLUSION

In summary, we investigate the utility of MWI in heterocyclization of *p*-aminobenzoic acid to synthesize a new series of imidazoles, pyrimidines, and thiazoles. A significant short reaction time, high pure products, and in addition to very good yields were observed with MW method. These results encourage us to do further work on such synthetic method.

EXPERIMENTAL

Melting points were measured using an Electro thermal IA 9100 apparatus (Stone, UK) with open capillary tube and are uncorrected. All experiments were carried out using drying solvents. Products were purified by recrystallization. All reaction was carried out under microwave (Discover™ by CEM, 2450 MHz, 20 bar, 300 W, 180°C). The IR spectrum (KBr discs) was recorded on a Pye Unicam Sp-^{3}-300 (UK) or a Shimadzu FTIR 8101 PC infrared spectrophotometer (Japan). The ^{1}H NMR 400 MHz and ^{13}C NMR 100 MHz spectrum were measured on a JEOL-JNM-LA spectrometer (Tokyo, Japan) using dimethyl sulfoxide as a solvent. All chemical shifts were expressed on the δ (ppm) scale using tetramethylslane as an internal standard reference. The coupling constant (J) values are given in Hz. Analytical data were obtained from the Micro analytical Center, Faculty of Pharmacy, Cairo University, Cairo, Egypt. The mass spectra were recorded on a MS-S988 instrument (New Jersey, USA) operating at 70 eV.

4-(2,4-Dioxoimidazolidin-1-yl)benzoic acid and 4-((1-(4-Carboxyphenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl)amino) benzoic acid (2a, **b**). ***Conventional method.*** A mixture of *p*-aminobenzoic acid **1** (0.01 mol), urea (0.01 mol), and chloroacetic acid (0.01 mol) was heated for about 20 min at 100°C, and then hot water was added, filter off compound **2a** on hot, and was crystallized from water. To separate the compound **2b, t**he filtrate was cooled, filter off, and crystallization from water.

Microwave method. A mixture of *p*-aminobenzoic acid **1** (1 mmol), urea (1 mmol), and chloroacetic acid (1 mmol) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave 5 min (Table 1). The reaction mixture was processed as described for the conventional method.

Compound 2a. Silver crystals; Yield: 60%; m.p. 255–260°C. IR (KBr): 3325, 3186 cm^{-1} (OH, NH), 1720, 1651 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6): δ = 4.67 (s, 2H, $H_{imidazol}$), 7.60 (d, 1H, J = 8.76 Hz, H_{Aryl}), 7.88 (d, 1H, J = 8.76 Hz, H_{Aryl}), 9.31 (s, 1H, NH), 12.71 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6): δ = 50.45 (SP^3-C), 113.0, 127.3, 130.3, 131.3, 168.1, 169.0 and 170.6 (SP^2-C). *Anal.* Calcd for $C_{10}H_8N_2O_4$ (220.18): C, 54.55; H, 3.66; N, 12.72. Found: C, 54.45; H, 3.54; N, 12.66.

Compound 2b. Pale brown; Yield: 60%; m.p. > 300°C. IR (KBr): 3367, 3186 cm^{-1} (OH, NH), 1774, 1716, 1678 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.29–8.10 (m, 9H, $H_{imidazol}$ and H_{Aryl}), 11.34 (s, 1H, NH, D_2O-exchangeable), 12.75 (b, 1H, COOH, D_2O-exchangeable). *Anal.* Calcd for $C_{17}H_{13}N_3O_5$ (339.30): C, 60.18; H, 3.86; N, 12.38. Found: C, 60.05; H, 3.77; N, 12.33.

4-(5-Amino-2-oxo-7-phenylimidazo[4,5-*d*]^{1,3}oxazin-1(2*H*)-yl)benzoic acid (3). ***Conventional method.*** A mixture of compound **2a** (0.01 mol), benzaldehyde (0.01 mol), and urea (0.01 mol) in acidic medium (2 mL hydrochloric acid) was refluxed for about 4 h and then pour the mixture into dilute acetic acid. The obtained precipitate was filtered and recrystallized from water/ethanol to give compound **3.** The golden crystal of compound **3** was obtained by filtration and recrystallization from water and ethanol.

Microwave method. A mixture of compound **2a** (1 mmol), benzaldehyde (1 mmol), and urea (1 mmol) in acidic medium (2 mL hydrochloric acid) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave 7 min (Table 1). The reaction mixture was processed as described for the conventional method.

The golden crystal of compound **3** was obtained by filtration and recrystallization from water and ethanol, yield: 50%; m.p. > 300°C. IR (KBr): 3325 cm^{-1} (OH, NH), 1670, 1654 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.57–7.95 (m, 9H, H_{Aryl}), 9.21 (s, 2H, NH_2, D_2O-exchangeable), 12.63 (b, 1H, COOH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ = 113.0, 117.8, 124.4, 127.0, 128.1, 128.8, 129.5, 130.2, 131.01, 144.1, 152.4, 167.5 and 169.0 (SP^2-C). Mass spectrometry: m/e = 347.80 (12%). *Anal.* Calcd for $C_{18}H_{12}N_4O4$ (348.31): C, 62.07; H, 3.47; N, 16.09. Found: C, 62.00; H, 3.35; N, 15.90.

4-(8-Oxo-6-phenyl-2-thioxo-2,3,8 and 9-tetrahydro-1*H*-purin-7(6*H*)-yl) benzoic acid (4). ***Conventional method.*** A mixture of compound **2a** (0.01 mol), benzaldehyde (0.01 mol), and thiourea (0.01 mol) in acidic medium (2 mL hydrochloric acid) was refluxed for about 4 h and then pour the mixture into dilute acetic acid. The obtained precipitate was filtered and recrystallized from water/ethanol to give compound **4.** The faint brown crystal of compound **4** was obtained by filtration and recrystallization from water and ethanol.

Microwave method. A mixture of compound **2a** (1 mmol), benzaldehyde (1 mmol), and thiourea (1 mmol) in acidic medium (2 mL hydrochloric acid) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave 8 min (Table 1). The reaction mixture was processed as described for the conventional method.

The faint brown crystal of compound **4** was obtained by filtration and recrystallization from water and ethanol, yield: 45%; m.p. > 300°C. IR (KBr): 3317 cm^{-1} (OH), 3186 cm^{-1} (NH), 1670 and 1654 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.55–7.95 (m, 9H, H_{Aryl}), 9.17 (s, 1H, NH, D_2O-exchangeable), 12.63 (b, 1H, COOH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ = 114.5, 117.6, 117.8, 118.8, 124.4, 127.8, 129.2, 130.6, 131.0, 144.1, 152.4, 162.7 and 167.4 (SP^2-C). *Anal.* Calcd for $C_{18}H_{14}N_4O_3S$ (366.39): C, 59.01; H, 3.85; N, 15.29. Found: C, 58.90; H, 3.72; N, 15.20.

4-(2,4-Dioxo-3-(phenyldiazenyl) imidazolidin-1-yl) benzoic acid (5). A mixture of compound **2a** (0.01 mol) was coupled with phenyl diazonium salt (0.01 mol) in ice bath to give the azo derivative **5**. The obtained precipitate was filtered and recrystallized from ethanol to give compound **5.**

The black crystal of compound **5** was obtained by filtration and recrystallization from water and ethanol, yield: 45%; m.p. > 300°C. IR (KBr): 3317 cm^{-1} (OH), 1670, 1654 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 4.69 (s, 2H, $H_{imidazol}$), 6.97–8.13 (m, 9H, H_{Aryl}), 10.61 (b, 1H, COOH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ = 50.47 (SP^3-C), 116.4, 117.7, 126.8, 128.8, 129.1, 129.7, 130.8, 134.6, 153.1, 168.1 and 169.2 (SP^2-C). *Anal.* Calcd for $C_{16}H_{12}N_4O_4$ (324.29): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.15; H, 3.68; N, 17.20.

4-(5-Imino-2-oxo-7-phenyl-2,3,4,5-tetrahydroimidazo[4,5-*d*][1,3]thiazin-1(7*H*)-yl)benzoic acid (6). ***Conventional method.*** A mixture of compound **2a** (0.01 mol), benzaldehyde (0.01 mol), and thiourea (0.01 mol) in sodium ethoxide solution [prepared from sodium metal

(0.23 g) in absolute ethanol (20 mL)]; was refluxed for about 4 h and then pour the mixture into water. The obtained precipitate was filtered and recrystallized from water/ethanol to give compound **6.** The flaxen crystal of compound **6** was obtained by filtration and recrystallization from ethanol.

Microwave method. A mixture of compound **2a** (1 mmol), benzaldehyde (1 mmol), and thiourea (1 mmol) in sodium ethoxide solution [prepared from sodium metal (0.023 g) in absolute ethanol (6 mL)] was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave 7 min (Table 1). The reaction mixture was processed as described for the conventional method.

The flaxen crystal of compound **6** was obtained by filtration and recrystallization from ethanol, yield: 60%; m.p. 292–295°C. IR (KBr): 3325, 3186 cm^{-1} (NH, OH), 1670, 1654 cm^{-1} (C═O) and 1589 cm^{-1} (C═N). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.57 (d, 2H, J = 8.72 Hz, H aryl), 7.88 (d, 2H, J = 8.72 Hz, H aryl), 9.17 (s, 2H, 2NH), 12.64 (s, 1H, OH). Mass spectrometry: m/e = 366.0 (5%). *Anal.* Calcd for $C_{18}H_{14}N_4O_3S$ (366.39): C, 59.01; H, 3.85; N, 15.29. Found: C, 58.90; H, 3.72; N, 15.20.

2-Benzamidobenzo[*d*]thiazole-6-carboxylic acid and 4-((5-phenyl-3*H*-1,2,4-oxathiazol-3-ylidene)amino) benzoic acid (7a, **b**). ***Conventional method.*** A mixture of benzoyl chloride (0.01 mol), ammonium thiocyanate (0.01 mol), and *p*-aminobenzoic acid (0.01 mol) was refluxed in acetone for 1 h. The obtained precipitate was filtered to thiourea derivative **7**. Approximately, 0.01 mol of compound **7** was refluxed for 0.5 h in Br_2/ACOH. The mixture was poured into water; it gave precipitate upon filtration we obtained compound **7a**, while compound **7b** was obtained when filtrate left to cool.

Microwave method. A mixture of benzoyl chloride (1 mmol), ammonium thiocynate (1 mmol), and *p*-aminobenzoic acid (1 mmol) in acetone (6 mL) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave 3 min (Table 1). The obtained compound **7** was microwave irradiated with Br_2 (1.1 mmol) for 3 min. The reaction mixture was processed as described for the conventional method.

Compound 7a. The faint yellow crystal of compound **7a** was obtained by filtration and recrystallization from ethanol and dimethylformamide (DMF), Yield: 55%; m.p. > 300°C. IR (KBr): 3174, 3132 cm^{-1} (OH, NH), 1678 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 4.20 (s, 2H, $H_{imidazol}$), 7.57–8.17 (m, 8H, H_{Aryl}), 8.86 (s, 1H, NH, D_2O-exchangeable), 13.03 (b, 1H, COOH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ = 49.0 (SP^3-C), 120.4, 124.3, 126.3, 127.8, 128.8, 129.1, 132.0, 132.1, 133.5, 1582.0, 162.4, 166.7and 167.5 (SP^2-C). *Anal.* Calcd for $C_{15}H_{10}N_2O_3S$ (298.32): C, 60.39; H, 3.38; N, 9.39. Found: C, 60.39; H, 3.38; N, 9.39.

Compound 7b. The gray crystal of compound **7b** was obtained by filtration and recrystallization from ethanol/DMF, Yield: 40%; m.p. 240–242°C. IR (KBr): 3371 cm^{-1} (OH), 1685 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.43–8.26 (m, 9H, H_{Aryl}), 12.81 (b, 1H, COOH, D_2O-exchangeable). *Anal.* Calcd for $C_{15}H_{10}N_2O_3S$ (298.32): C, 60.39; H, 3.38; N, 9.39. Found: C, 60.30; H, 3.28; N, 9.25.

Synthesis of *N*-(6-(1*H*-benzo[*d*]imidazol-2-yl) benzo[*d*] thiazol-2-yl)benzamide (8) and *N*-(6-(6-methyl-1*H*-benzo[*d*] imidazol-2-yl) benzo[*d*]thiazol-2-yl) benzamide (9). ***Conventional method.*** A mixture of **7a** (0.01 mol) and phenylenediamine or 4-methyl phenylenediamine (0.01 mol) was refluxed for 4 h in DMF. After then, the mixture was poured into water. The obtained precipitate was filtered to give compounds **8** and **9**.

Microwave method. A mixture of **7a** (0.01 mol) and phenylenediamine or 4-methyl phenylenediamine (0.01 mol) in DMF (6 mL) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave for 10 and 12 min (Table 1). The reaction mixture was processed as described for the conventional method.

Compound 8. The canary crystal of compound **8** was obtained by filtration and recrystallization from ethanol and DMF, yield: 35%; m. p. 286–290°C. IR (KBr): 3340, 3170 cm^{-1} (NH), 1666 cm^{-1} (C═O). ^{1}H NMR (DMSO-d_6/D_2O): δ = 7.11–8.15 (m, 12H, H_{Aryl}), 12.25, 12.51 (2 s, 2H, 2NH, D_2O-exchangeable). Mass spectrometry: m/e = 369.98 (7%). *Anal.* Calcd for $C_{21}H_{14}N_4OS$ (370.43): C, 68.09; H, 3.81; N, 15.12. Found: C, 68.00; H, 3.75; N, 15.05.

Compound 9. The brown crystal of compound **9** was obtained by filtration and recrystallization from ethanol and DMF, yield: 30%; m p. 252–254°C. IR (KBr): 3336, 3178 cm^{-1} (NH), 1658 cm^{-1} (C═O). ^{1}HNMR (DMSO-d_6/D_2O): δ = 2.39 (s, 3H, H_{methyl}), 6.95–8.15 (m, 12H, H_{Aryl}), 12.18, 12.21 (2 s, 2H, 2NH, D_2O-exchangeable). *Anal.* Calcd for $C_{22}H_{16}N_4OS$ (384.45): C, 68.73; H, 4.19; N, 14.57. Found: C, 68.60; H, 4.10; N, 14.45.

4-(5-Acetyl-4-(4-hydroxyphenyl)-6-methyl-2-oxopyrimidin-1(2*H*)-yl)benzoic acid, 4-(5-acetyl-4-(4-hydroxyphenyl)-2,6-dioxo-2,3-dihydropyrimidin-1(6*H*)-yl)benzoic acid, and 4-(2,4,6-trioxotetrahydropyrimidin-1(2*H*)-yl)benzoic acid (10a–**c**). ***Conventional method.*** A mixture of *p*-aminobenzoic acid (0.01 mol) and potassium cyanate was refluxed for 1 h to give compound **10**. The compound **10** was used in further step without purification.

Microwave method. A mixture of *p*-aminobenzoic acid (1 mmol) and potassium cyanate (1.1 mmol) was sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave (Table 1). The reaction mixture was processed as described for the conventional method.

Conventional method. A mixture of compound **10** (0.01 mol), salicyladehyde (0.01 mol), and acetyl acetone, ethyl acetoacetate, or diethyl malonate (0.01 mol) in acidic medium (2 mL hydrochloric acid) was refluxed for 6 h; the obtained solid was crystalized from ethanol.

Microwave method. A mixture of compound **10** (1 mmol), salicylaldehyde (1 mmol), and acetyl acetone, ethyl acetoacetate, or diethyl malonate (1 mmol) in acidic medium (2 ml hydrochloric acid) as sealed in a 10 mL septum reaction vial with magnetic stirrer bar and irradiated with microwave (Table 1). The reaction mixture was processed as described for the conventional method.

Compound 10a. Dark brown powder of compound **10a** was obtained by filtration and recrystallization from ethanol, yield: 45%; m.p. 208–211°C. IR (KBr, υ, cm^{-1}): 3232 (OH), 1716, 1662 (C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.74, 2.89 (2 s, 1H, $2CH_3$), 6.77–7.52 (m, 8H, Ar─H), 7.96 (s, 1H, OH), 9.63 (s, 1H, OH). Mass spectrometry: m/e = 364 (22%). *Anal.* Calcd for $C_{20}H_{16}N_2O_5$ (364.35): C, 65.93; H, 4.43; N, 7.69. Found: C, 65.85; H, 4.40; N, 7.60.

Compound 10b. Black powder of compound **10b** was obtained by filtration and recrystallization from ethanol, yield: 35%; m.p. 196–199°C. IR (KBr, υ, cm^{-1}): 3430, 3194 and 1685 (OH, NH and C═O). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.3 (s, 3H, CH_3), 6.76–7.53 (m, 8H, Ar─H), 7.95 (s, 1H, OH), 8.20 (s, 1H, NH), 9.04 (s, 1H, OH). ^{13}CNMR (100 MHz, DMSO-d6) δ (ppm): 14.73 (CH_3), 117.1, 126.3, 126.8, 127.0, 127.9, 128.7, 130.7, 132.1, 133.0, 138.0, 156.0, 163.2, 164.1, 168.5 (SP^2-C). *Anal.* Calcd for C19H14N2O6 (366.32): C, 62.30; H, 3.85; N, 7.65. Found: C, 62.22; H, 3.75; N, 7.55.

Compound 10c. Yellow crystal of compound **10c** was obtained by filtration and recrystallization from ethanol, yield: 25%; m.p. 180–182°C. IR (KBr, υ, cm^{-1}): 3367, 3271, 1708 and 1604 (OH, NH, C═O and C═N). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.3 (t, 3H, J = 6.80 Hz, CH_3CH_2), 4.33(q, 2H, J = 6.80 Hz, CH_3CH_2), 6.55–7.60 (m, 8H, Ar─H), 7.89 (s, 1H, OH), 8.61(s, 1H, NH), 10.05(s, 1H, OH). *Anal.* Calcd for $C_{11}H_8N_2O_5$ (248.19): C, 53.23; H, 3.25; N, 11.29. Found: C, 53.20; H, 3.15; N, 11.20.

REFERENCES AND NOTES

[1] Gupta, P.; Gupta, J. K. Chem Sci J 2015, 6, 1.

[2] Brown, E. G. Ring Nitrogen and Key Biomolecules; Kluwer Academic Press: U. K (Chapter 2), 1998.

[3] Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. A. Drugs 2009, 7, 705.

[4] King, F. E.; Kidd, D. A. A. Org Prep Proceed Int 1948, 162, 776.

[5] Quahog, J.; Hernandez, P.; Insuasty, B.; Abonia, R.; Cobo, J.; Sanchez, A.; Nogueras, M.; Low, J. N. J Chem Soc Perkin Trans 2002, 4, 555.

[6] Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. Org Lett 2012, 14, 5948.

[7] Yang, Z.; Chen, X.; Wang, S.; Liu, J.; Xie, K.; Wang, A.; Tan, Z. J Org Chem 2012, 77, 7086.

[8] Bastug, G.; Eviolitte, C.; Markó, I. E. Org Lett 2012, 14, 3502.

[9] Malik, V.; Singh, P.; Kumar, S. Tetrahedron 2006, 62, 5944.

[10] Novikov, M. S.; Buckheit, R. W. Jr.; Temburnikar, K.; Khandazhinskaya, A. L.; Ivanov, A. V.; Seley-Radtke, K. L. Bioorg Med Chem 2010, 18, 8310.

[11] Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. Eur J Med Chem 2009, 44, 2651.

[12] Sondhi, S. M.; Jain, S.; Dinodia, M.; Shukla, R.; Raghubir, R. Bioorg Med Chem 2007, 15, 3334.

[13] Sondhi, S. M.; Dinodia, M.; Rani, R.; Shukla, R.; Raghubir, R. Indian J Chem 2009, 49b, 273.

[14] Russowsky, D.; Canto, R. F. S.; Sanches, S. A. A.; D'Oca, M. G. M. Bioorg Chem 2006, 34, 173.

[15] Waseem, M. A.; Lone, A. M.; Ibad, F.; Ibad, A.; Yadav, V. B.; Ansari, K.; Shairjogrey, B. A.; Watal, G.; Siddiqui, I. R. J Heterocyclic Chem 2017, 54, 1061.

[16] El-Sayed, H. A.; Moustafa, A. H.; Haikal, A. Z.; El-Ashry, E. S. H. Nucleosides Nucleotides Nucleic Acids 2009, 28, 184.

[17] El-Sayed, H. A.; Moustafa, A. H.; Haikal, A. Z.; Abu-El-Halawa, R.; El Ashry, E. H. Eur J Med Chem 2011, 46, 2948.

[18] Tierney, J. P.; Lidstrom, P. Microwave Assisted Organic Synthesis; Blackwell: Oxford, 2005.

[19] Kappe, C. O. Angew Chem Int Ed, 43, 2004.

[20] Kappe, C. O. Angew Chem Int Ed, 116, 2004.

[21] Selim, Y.; EL-Ahwany, M. Chem Heterocyc Comp 2017, 53, 867.