Received: 11 May 2019 | Revised: 13 August 2019 | Accepted: 27 August 2019

DOI: 10.1002/jhet.3737

ARTICLE

WILEY

Synthesis of novel hexahydroquinolines and 6-amino-2-oxopyridine-3,5-dicarbonitriles incorporating sulfamethoxazole via [3 + 3] annulation

Amr M. Abdelmoniem | **Mohamed Gamal Mohamed Abdelrahman** | **Said Ahmed Soliman Ghozlan** | **Ismail A. Abdelhamid**

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Correspondence
Ismail A. Abdelhamid, Department of Chemistry, Faculty of Science, Cairo University, PO 12613 Giza, Egypt.
Email: ismail_shafy@yahoo.com

Abstract

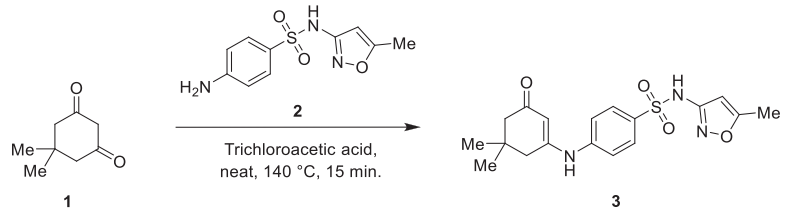
Cyclic enaminone and cyanoacetamide derivative with incorporated sulfamethoxazole moiety were prepared. Their reactions with arylidenemalononitrile derivatives in ethanol or pyridine/piperidine at reflux yielded the corresponding hexahydroquinoline and 6-amino-2-oxopyridine-3,5-dicarbonitrile derivatives incorporating sulfamethoxazole. The mechanism and structural elucidation of products were discussed.

1 | INTRODUCTION

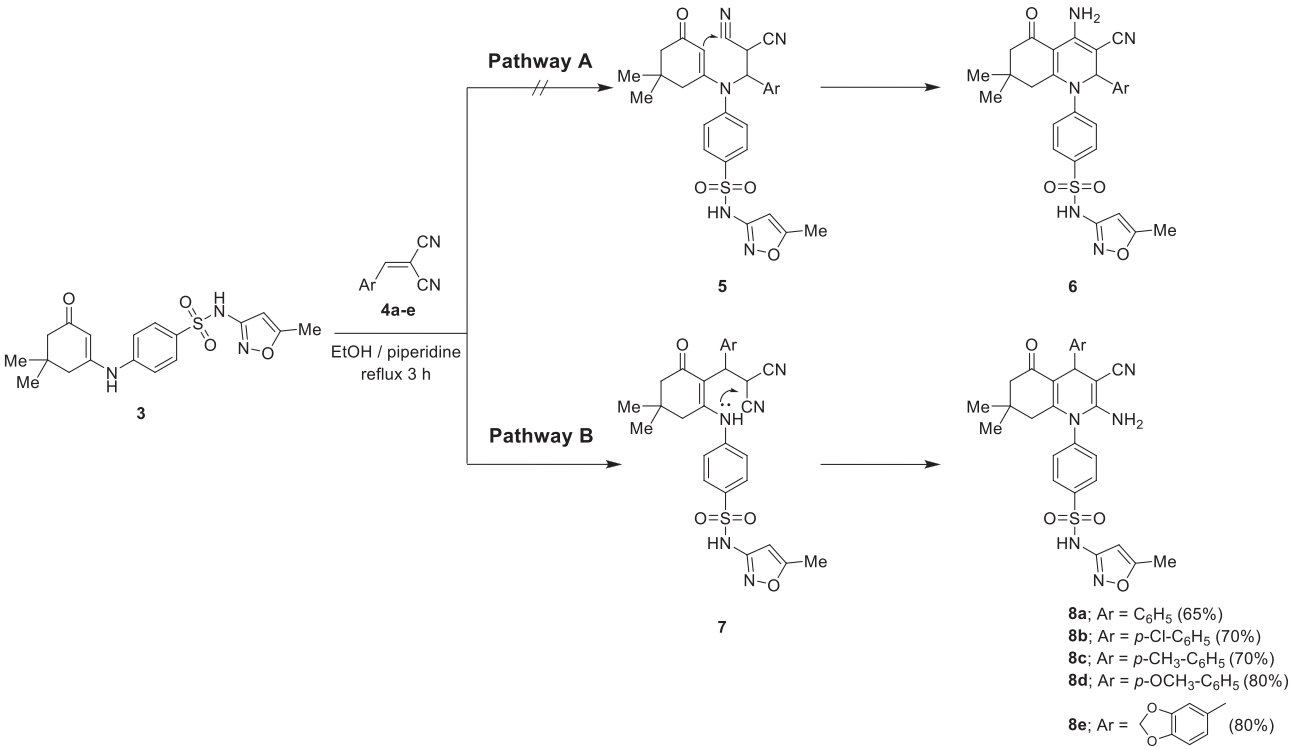
Sulfamethoxazole is a chemotherapeutic drug that exhibits a wide range of pharmacological and biological activities that include antimicrobial[1–5] and anticancer agents.[6,7] Also, it is used in the treatment of urinary tract infections.[1,8] In addition, pyridine derivatives have attracted a particular interest over the past years due to their various biological activities, including antiviral,[9] antihistaminic,[10] antihypertensive,[11] anti-inflammatory agents,[12] and antitumors.[13] Furthermore, quinolines are unique fused six-membered heterogeneous pharmacological compounds that offered a wide range of activities such as antibacterial, antitumor, anti-inflammatory, antiasthmatic, antimalarial, antituberculosis, and antihypertensive properties.[14–19] On the other hand, due to the excellent mechanical characteristics of quinolines, they have found significant use in electronics, optoelectronics, and polymer chemistry.[20,21] Self-hierarchical assembly of quinoline copolymers into meso- and nano-structures enhanced greatly their photonic and electronic features.[22] Hexahydroquinolines exhibited potent and promising cytotoxic, antibacterial, myorelaxant, calcium channel modulatory, and neuroprotective activities.[23–28] 1,4-Dihydropridines have emerged as important derivatives that selectively prohibit L-type calcium channels and act as well as one of the most common therapeutic agents for the treatment of cardiovascular diseases, including hypertension.[29,30]

2 | RESULTS AND DISCUSSION

In continuation to our interest in the C—C bond formation reactions,[31–45] the possibility of [3 + 3] atom combination reaction of the cyclic enamine incorporating sulfamethoxazole with α,β-unsaturated nitriles through Michael addition reaction was studied. First, the cyclic enamine **3** was prepared via the reaction of dimedone **1** with sulfamethoxazole **2** according to the procedure reported in the literature by us[33–35,44–46] and by others[47] (Scheme 1). The Michael addition reaction of the cyclic enamine **3** with arylidenemalononitriles **4a-e** was then investigated. In principle, for this type of reaction, there are two possible isomeric structures for the product. The product is either 4-aminohexahydroquinoline-3-carbonitrile **6** that results from initial addition of NH to the activated double bond in compound **4** to give **5** that readily cyclizes to **6** (pathway A) or 2-aminohexahydroquinoline-3-carbonitrile **8** that results from the initial addition of enamine CH to the activated double bond in compound **4** to yield **7** that



SCHEME 1 Synthesis of cyclic enamine incorporating sulfamethoxazole **3**.



SCHEME 2 The Michael addition reaction of the cyclic enamine **3** with arylidenemalononitriles **4a-e**.

readily cyclizes to **8** (pathway B) (Scheme 2). Although the ^{1}H and ^{13}C-NMR cannot simply differentiate between the two isomers, we indubitably solved this problem and assumed that compound **8** to be the correct structure based on previous chemical elucidation[33,44,45] and heteronuclear multiple bond correlation (HMBC) spectral analysis[35] of some related compounds. In addition, we managed to confirm the structure through HMBC spectrum of compound **8c**. The HMBC spectrum revealed cross-correlation peaks between quinoline H4 at δ 4.41 ppm and carbonyl group at δ 195.3 ppm which is copatible with the proposed structure (Figure 1). The mass spectrum of **8c** showed a molecular ion peak at *m/z* 543 [M^+]. The IR spectrum revealed broad absorption bands at ν_{max} 3399, 3324, and 3223 cm^{-1} for the NH and NH_2 groups. In addition, it indicated a characteristic band at ν_{max} 2183 cm^{-1} for the cyano group and a strong stretching band at ν_{max} 1648 cm^{-1} for the carbonyl group. The ^{1}H NMR displayed a singlet at δ 4.41 ppm for quinoline-*H*4 and a singlet at δ 5.86 ppm for isoxazole-*H*4. It also featured a singlet at δ 5.28 ppm for the amino group. The aromatic protons appeared as multiplets at δ 7.13 to 7.14 ppm. The broad signal at δ 8.49 ppm was assigned to the NH group.

It is worth mentioning that the delocalization of nitrogen lone pair in enamine **3** develops a negative charge on the β-carbon (intermediate **3(II)**). Michael addition reaction of **3(II)** to the delocalized double bond in arylidene derivatives **4** in the presence of a basic catalyst (acts as a carrier for the labile hydrogen) leads to the formation of the Michael adduct **9**. Intermediate **9** abstracts the proton again from the catalyst, leading to the formation of the intermediate **10** which tautomerizes into **7**. Nucleophilic addition of NH to the cyano group affords the cyclic intermediate **11**. Which tautomerizes into compound **8** (Scheme 3).

In an extension to this work, the 2-cyanoacetamide incorporating sulfamethoxazole group **13** was chosen as a key starting material in Michael addition reaction for synthesis of a variety of novel cyanopyridone derivatives. It is

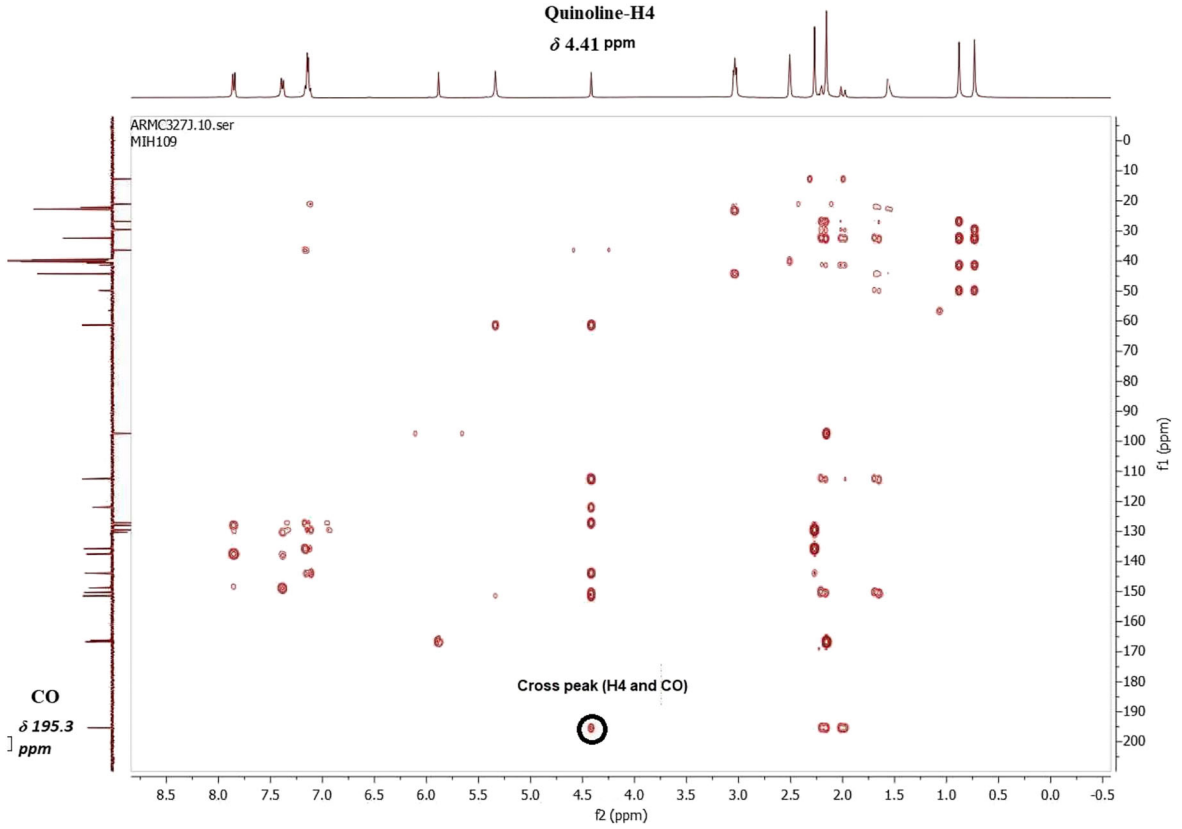
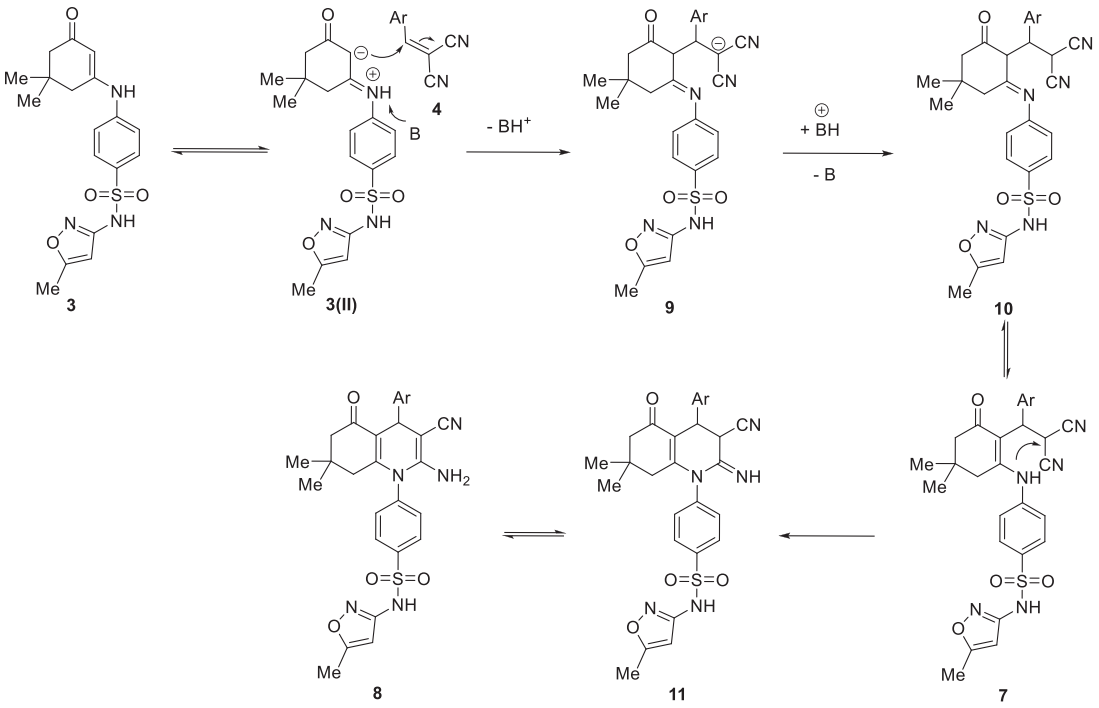


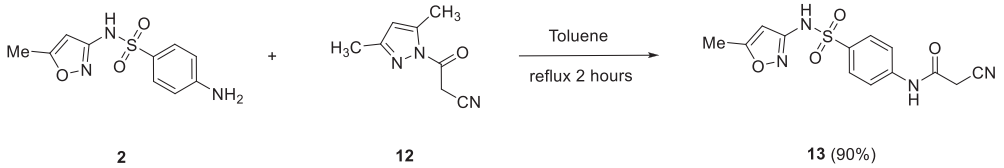
FIGURE 1 The heteronuclear multiple bond correlation (HMBC) spectrum of compound **8c** [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 3 A plausible mechanism of the reaction of enamine **3** with arylidenemalononitriile derivatives **4**.

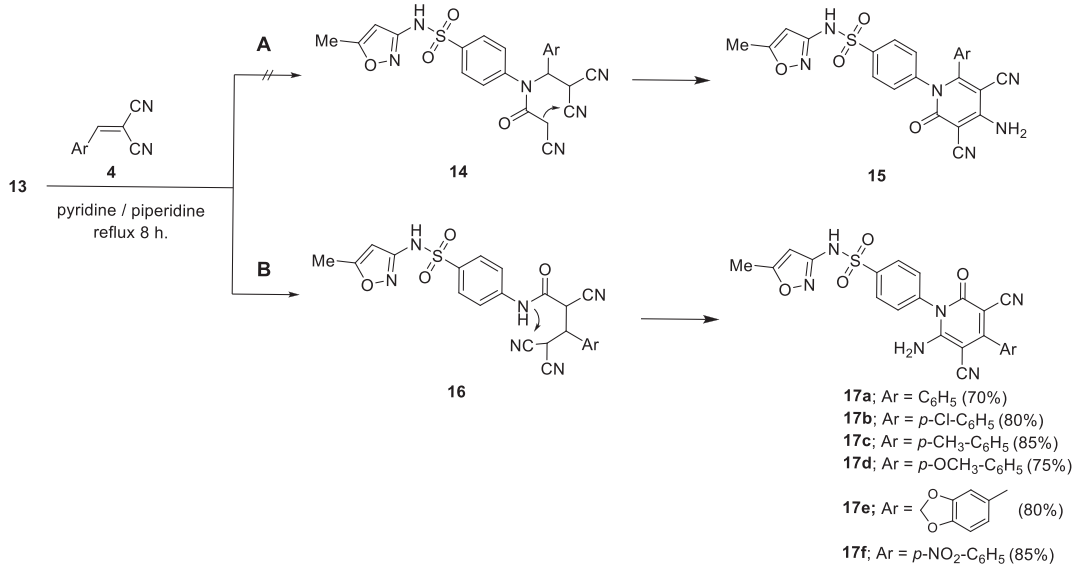
prepared via the cyanoacylation of the sulfamethoxazole **2** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **12** in toluene at reflux according to our recently reported procedure[48,49] (Scheme 4). The Michael addition reaction of 2-cyanoacetamide **13** with unsaturated nitriles **4** was then explored. Thus, the reaction of compound **13** with arylidenemalononitriles **4a-f** can generally lead to the formation of either 4-aminopyridine-3,5-dicarbonitrile **15** (pathway A) or its isomeric structure 6-aminopyridine-3,5-dicarbonitrile **17** (pathway B) through the intermediacy of **14** or **16**, respectively (Scheme 5). The constitution of pyridine derivatives **17** was unambiguously confirmed through careful comparison with spectral data of some similar reported structures.[49–51] For instance, the mass spectrum of compound **17c** displayed a molecular ion peak at *m/z* 486. The IR spectrum exhibited three absorption bands at ν_{max} 3366, 3315, and 3208 cm^{-1} for the NH and NH_2 groups. It showed characteristic bands at ν_{max} 2215 and 1634 cm^{-1} for the cyano and carbonyl groups, respectively. Moreover, the ^1H NMR spectrum of **17c** indicated the signals of aromatic protons at δ 7.37 to 8.06 ppm, together with a broad peak centered at δ 8.04 ppm for the amino group. Additionally, it featured a broad singlet for the NH at δ 11.65 ppm.

It is also noteworthy that the reaction of aldehyde **18** with cyanoacetamide **13** afforded the cyanoacrylamide **19**. The subsequent reaction with malononitrile **20** resulted in the formation of the target product **17**. In support of this viewpoint, we managed to isolate the Knoevenagel condensation in some cases **19a,b**[51] and were found in agreement with the reported literature (Scheme 6).



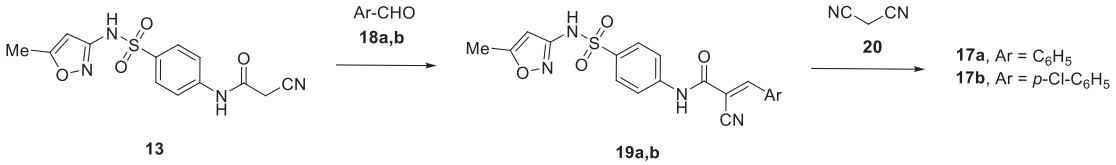
2 **12** **13** (90%)

SCHEME 4 Synthesis of 2-cyanoacetamide incorporating sulfamethoxazole group **13**.



17a; Ar = C_6H_5 (70%)
17b; Ar = *p*-Cl-C_6H_5 (80%)
17c; Ar = *p*-CH_3-C_6H_5 (85%)
17d; Ar = *p*-OCH_3-C_6H_5 (75%)
17e; Ar = (80%)
17f; Ar = *p*-NO_2-C_6H_5 (85%)

SCHEME 5 The Michael addition reaction of 2-cyanoacetamide **13** with unsaturated nitriles **4**.



17a, Ar = C_6H_5
17b, Ar = *p*-Cl-C_6H_5

SCHEME 6 An alternative synthesis of **17** employing Knoevenagel adducts **19a-f** and malononitrile **20**

3 | CONCLUSIONS

Cyclic enaminones and 2-cyanoacetamide were used as versatile precursors for the synthesis of a novel series of the respective hexahydroquinoline and 6-amino-2-oxopyridine-3,5-dicarbonitrile derivatives incorporating sulfamethoxazole derivatives.

4 | EXPERIMENTAL

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a Fourier-transform infrared (FTIR) Bruker-vector 22 spectrophotometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO–*d*6 as solvent on Varian Gemini NMR spectrometer at 300 and 75 MHz, respectively, using tetramethylsilane (TMS) as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS-QP 1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro Analytical Center, Cairo University.

4.1 | 4-((5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)amino)-*N*-(5-methylisoxazol-3-yl) benzenesulfonamide (3)

A mixture of dimedone **1** (1000 mg, 7.13 mmol) and sulfamethaxazole **2** (1804 mg, 7.13 mmol) and trichloroacetic acid (250 mg, 153 mmol) was heated in an oil bath at 140°C for 15 minutes. The crude product was isolated and then purified by crystallization from ethanol (15 mL) to yield the pure compound **3** as orange crystals (338 mg, 90%). Mp 118°C to 120°C. IR (KBr): ν_{max}/cm^{-1} 3333, 3379, (2NH), 1523 (CO), 1405, 1161 (SO_2). ^{1}H NMR (DMSO-d$_6$): δ/ppm 1.02 (s, 6H, 2CH_3), 2.10 (s, 2H, CH_2), 2.30 (s, 3H, isoxazole-CH_3), 2.40 (s, 2H, CH_2), 5.55 (s, 1H, isoxazole-*H*), 6.12 (s, 1H, enamine-C*H*), 7.33–7.36 (d, J = 8.8 Hz, 2H, Ar*H*), 7.78–7.82 (d, J = 8.8 Hz, 2H, Ar*H*), 9.09 (s, 1H, N*H*), 11.35 (br, 1H, N*H*). MS (EI, 70 eV): *m/z* 375 [M]$^+$. Anal. Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.84; H, 5.45; N, 11.51.

4.2 | General procedure for synthesis of compounds (8a-e)

A mixture of β-enaminone **3** (375 mg, 1 mmol) and arylidene malononitrile **4a-e** (1 mmol) was heated at reflux in ethanol (20 mL) containing piperidine (0.2 mL, 2 mmol) for 3 hours. The excess solvent was evaporated under reduced pressure and the collected crude product was purified by crystallization from EtOH/dioxane (5 mL, 3:1, v/v).

4.3 | 4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)-*N*-(5-methylisoxazol-3-yl) benzenesulfonamide (8a)

Off-white crystals (344 mg, 65%). Mp 117°C to 120°C. IR (KBr): ν_{max}/cm^{-1} 3401, 3330, 3226 (NH and NH_2), 2183 (C≡N), 1649 (CO), 1374, 1134 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 0.73 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.64 to 1.70 (m, 2H, CH_2), 1.97 to 2.21 (m, 2H, CH_2), 2.17 (s, 3H, isoxazole-CH_3), 4.45 (s, 1H, quinoline-*H*4), 5.92 (s, 1H, isoxazole-*H*), 6.55 (s, 2H, NH_2), 7.21 to 7.88 (m, 9H, Ar*H*), 8.41 (br, 1H, N*H*). MS (EI, 70 eV): *m/z* 529 [M]$^+$. Anal. Calcd. for $C_{28}H_{27}N_5O_4S$: C, 63.50; H, 5.14; N, 13.22. Found: C, 63.14; H, 5.38; N, 12.95.

4.4 | 4-(2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (8b)

Off-white crystals (394 mg, 70%). Mp 238°C to 242°C; IR (KBr): ν_{max}/cm^{-1} 3398, 3322, 3222 (NH and NH_2), 2183 (C≡N), 1648 (CO), 1375, 1131 (SO_2). ^{1}H NMR (DMSO-d$_6$): δ/ppm 0.72 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.55 to 1.63 (m, 2H, CH_2), 2.02 to 2.20 (m, 2H, CH_2), 2.14 (s, 3H, isoxazole-CH_3), 4.46 (s, H, quinoline-*H*4), 5.38 (s, 2H, NH_2), 5.87 (s, 1H, isoxazole-*H*), 7.27 to 7.85 (m, 8H, Ar*H*), 8.61 (br, 1H, N*H*). MS (EI, 70 eV): *m/z* 563 [M]$^+$. Anal. Calcd. for $C_{28}H_{26}ClN_5O_4S$: C, 59.62; H, 4.65; Cl, 6.28; N, 12.42. Found: C, 59.41; H, 4.80; Cl, 6.64; N, 12.15.

4.5 | 4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)-*N*-(5-methylisoxazol-3-yl) benzenesulfonamide (8c)

Pale yellow crystals (380 mg, 70%). Mp 237°C to 239°C. IR (KBr): ν_{max}/cm^{-1} 3399, 3324, 3223 (NH and NH_2), 2183 (C≡N), 1648 (CO), 1375, 1131 (SO_2). ^{1}H NMR (DMSO-d$_6$): δ/ppm 0.73 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.56 to 1.65 (m, 2H, CH_2), 2.00 to 2.20 (s, 2H, CH_2), 2.14 (s, 3H, isoxazole-CH_3), 2.26 (s, 3H, *p*-tolyl-CH_3), 4.41 (s, H,

quinoline-*H*4), 5.28 (s, 2H, NH_2), 5.86 (s, 1H, isoxazole-*H*), 7.13 to 7.14 (m, 4H, Ar*H*), 7.35 to 7.37 (d, J = 8.8 Hz, 2H, Ar*H*), 7.82–7.85 (d, J = 8.8 Hz, 2H, Ar*H*), 8.49 (br, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.7, 21.1, 22.7, 26.7, 29.4, 32.4, 36.3, 49.8, 61.4, 97.4, 112.6, 121.9, 127.1, 127.9, 129.4, 130.3, 135.7, 137.5, 143.9, 148.8, 150.3, 151.5, 166.2, 166.7, 195.3. MS (EI, 70 eV): *m/z* 543 [M]$^+$. Anal. Calcd. for $C_{29}H_{29}N_5O_4S$: C, 64.07; H, 5.38; N, 12.88. Found: C, 63.84; H, 5.52; N, 12.65.

4.6 | 4-(2-Amino-3-cyano-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (8d)

Yellow crystals (447 mg, 80%). Mp 228°C to 230°C. IR (KBr): ν_{max}/cm^{-1} 3405, 3331, (NH and NH_2), 2182 (C≡N), 1650 (CO), 1378, 1129 (SO_2). ^{1}H NMR (DMSO-d_6): δ/ppm 0.73 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.50 to 1.64 (m, 2H, CH_2), 1.98 to 2.21 (m, 2H, CH_2), 2.14 (s, 3H, isoxazole-CH_3), 3.73 (s, 3H, OCH_3), 4.4 (s, H, quinoline-*H*), 5.28 (s, 2H, NH_2), 5.87 (s, 1H, isoxazole-*H*), 6.86 to 6.89 (d, J = 8.8 Hz, 2H, Ar*H*), 7.16 to 7.19 (d, J = 8.8 Hz, 2H, Ar*H*), 7.35 to 7.38 (d, J = 8.8 Hz, 2H, ArH), 7.82 to 7.85 (d, J = 8.8 Hz, 2H, ArH), 8.72 (br, 1H, N*H*). MS (EI, 70 eV): *m/z* 559 [M]$^+$. Anal. Calcd. for $C_{29}H_{29}N_5O_5S$: C, 62.24; H, 5.22; N, 12.51. Found: C, 61.92; H, 5.51; N, 12.83.

4.7 | 4-(2-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (8e)

Off-white crystals (459 mg, 80%). Mp 234°C to 236°C. IR (KBr): ν_{max}/cm^{-1} 3391, 3322, 3217 (NH and NH_2), 2183 (C≡N), 1649 (CO), 1383, 1134 (SO_2). ^{1}H NMR (DMSO-d_6): δ/ppm 0.75 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.59 to 1.63 (m, 2H, CH_2), 1.99 to 2.19 (m, 2H, CH_2), 2.14 (s, 3H, isoxazole-CH_3), 4.39 (s, 1H, quinoline-*H*4), 5.30 (s, 2H, NH_2), 5.86 (s, 2H, OCH_2O), 5.98 (s, H, isoxazole-*H*), 6.72 to 6.75 (d, J = 8.8 Hz, 2H, Ar*H*), 6.76 (s, 1H, Ar*H*), 6.83 to 6.85 (d, J = 8.8 Hz, 1H, Ar*H*), 7.33 to 7.36 (d, J = 8.8 Hz, 2H, Ar*H*), 7.82 to 7.85 (d, J = 8.8 Hz, 2H, Ar*H*), 8.57 (br, 1H, N*H*). MS (EI, 70 eV): *m/z* 573 [M]$^+$. Anal. Calcd. for $C_{29}H_{27}N_5O_6S$: C, 60.79; H, 4.74; N, 12.21. Found: C, 61.04; H, 4.37; N, 12.45.

4.8 | 2-Cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (13)

A mixture of sulphamethaxazole (2533 mg, 10 mmol) **2** and 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **12** (1630 mg, 10 mmol) in dry toluene (20 mL) was heated at reflux for 3 hours. The crude isolated product was purified by crystallization with ethanol (10 ml) to give white crystals (2880 mg, 90%). Mp 216°C to 218°C. IR (KBr): ν_{max}/cm^{-1} 3331, 3279 (2NH), 2264 (C≡N), 1690 (C=O), 1397, 1167 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 2.30 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 6.13 (s, 1H, isoxazole-C*H*), 7.73 to 7.75 (d, J = 8.8 Hz, 2H, Ar*H*), 7.82 to 7.85 (d, J = 8.8 Hz, 2H, Ar*H*), 10.71 (s, 1H, CON*H*), 11.37 (br, 1H, SO_2N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.5, 27.5, 95.9, 116.1, 119.6, 128.7, 134.4, 143.1, 158.0, 162.5, 170.9. MS (EI, 70 eV): 320 [M$^+$], Anal. Calcd. for $C_{13}H_{12}N_4O_4S$: C, 48.75; H, 3.78; N, 17.49. Found C, 48.46; H, 3.53; N, 17.28;

4.9 | General procedure for the synthesis of compounds (17a-f)

Equimolar amounts of **13** (320 mg, 1 mmol) and the appropriate arylidene malononitrile **4** (1 mmol) was dissolved in pyridine (5 mL). Piperidine (0.2 mL, 2 mmol) was added and the reaction mixture was heated at reflux for 3 hours. Then the resulting solution was poured onto ice-cold HCl (10 N, 30 mL). The crude isolated product was crystallized from EtOH/dioxane (5 mL, 1:1, v/v).

4.10 | 4-(6-Amino-3,5-dicyano-2-oxo-4-phenylpyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17a)

Gray crystals (330 mg, 70%). Mp. > 300°C. IR (KBr): ν_{max}/cm^{-1} 3363, 3317, 3213 (NH and NH_2), 2219 (C≡N), 1631 (CO), 1408, 1169 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm 2.34 (s, 3H, CH_3), 6.25 (s, 1H, C*H*), 7.53 (s, 2H, NH_2), 7.55 to 7.60 (m, 5H, Ar*H*), 7.67 to 7.69 (d, J = 8.8 Hz, 2H, Ar*H*), 8.05 to 8.07 (br d, J = 8.8 Hz, 4H, Ar*H* and NH_2), 11.66 (br, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.6, 76.0, 95.9, 116.1, 116.6, 128.4, 129.2, 129.35, 130.63, 130.87, 135.1, 138.68, 141.52, 157.39, 157.87, 159.89, 162.05, 170.94. MS (EI, 70 eV): 472.1 [M$^+$]. Anal. Calcd. for $C_{23}H_{16}N_6O_4S$: C, 58.47; H, 3.41; N, 17.79. Found: C, 58.68; H, 3.53; N, 17.54.

4.11 | 4-(6-Amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxopyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17b)

Yellow crystals (405 mg, 80%). Mp 291°C to 293°C. IR (KBr): ν_{max}/cm^{-1} 3330, 3317, 3204 (NH and NH_2), 2219 (C≡N), 1637 (CO), 1408, 1169 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 2.34 (s, 3H, CH_3), 6.24 (s, 1H, C*H*), 7.57 to 7.59 (d, J = 8.8 Hz, 2H, Ar*H*), 7.65 to 7.67 (d, J = 8.8 Hz, 2H, Ar*H*), 7.67 to 7.69 (d, J = 8.8 Hz, 2H, Ar*H*), 8.06 (d, J = 8.8 Hz, 2H, Ar*H*), 8.05 to 8.07 (d, 2H, Ar*H*), 8.14 (br, 2H, NH_2), 11.66 (br, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.6, 76.0, 95.9, 116.0, 116.5, 129.4, 129.5, 130.4, 130.6, 133.9, 135.7, 138.6, 141.5, 157.4, 157.8, 159.8, 160.9, 171.0. MS (EI, 70 eV): 506 [M^+], Anal. Calcd. for $C_{23}H_{15}ClN_6O_4S$: C, 54.50; H, 2.98; Cl, 6.99; N, 16.58. Found: C, 54.75; H, 3.20; Cl, 6.72; N, 16.39.

4.12 | 4-(6-Amino-3,5-dicyano-2-oxo-4-(*p*-tolyl)pyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17c)

Pale yellow crystals (413.2 mg, 85%). Mp > 300°C. IR (KBr): ν_{max}/cm^{-1} 3366, 3315, 3208 (NH and NH_2), 2215 (C≡N), 1634 (CO), 1343, 1167 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 2.33 (s, 3H, isoxazole-CH_3), 2.41 (s, 3H, *p*-tolyl-CH_3), 6.23 (s, 1H, CH), 7.37 to 7.45 (m, 4H, J = 8.8 Hz, Ar*H*), 7.65 to 7.68 (d, J = 8.8 Hz, 2H, Ar*H*), 8.03 to 8.06 (br d, J = 8.8 Hz, 4H, Ar*H* and NH_2), 11.65 (br, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.1, 21.0, 75.5, 95.5, 115.7, 116.3, 127.9, 128.9, 129.2, 130.2, 131.7, 138.2, 140.3, 141.1, 156.9, 157.4, 159.5, 161.6, 170.5. MS (EI, 70 eV): 486 [M^+], Anal. Calcd. for $C_{24}H_{18}N_6O_4S$: C, 59.25; H, 3.73; N, 17.27. Found: C, 58.98; H, 3.48; N, 17.56.

4.13 | 4-(6-Amino-3,5-dicyano-4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17d)

Light yellow crystals (376.5 mg, 75%). Mp 285°C to 287°C. IR (KBr): ν_{max}/cm^{-1} 3400, 3317, 3315 (NH and NH_2), 2213 (C≡N), 1606 (CO), 1410, 1174 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 2.34 (s, 3H, CH_3), 3.87 (S, 3H, OCH_3), 6.25 (s, 1H, C*H*), 7.13 to 7.15 (d, J = 8.8 Hz, 2H, Ar*H*), 7.51 to 7.53 (d, J = 8.8 Hz, 2H, Ar*H*), 7.66 to 7.68 (d, J = 8.8 Hz, 2H, Ar*H*), 8.04 to 8.07 (br d, J = 8.8 Hz, 4H, Ar*H* and NH_2), 11.65 (br, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.6, 55.8, 76.0, 95.9, 114.5, 116.4, 116.9, 127.0, 129.3, 130.3, 130.6, 138.7, 141.5, 157.4, 157.8, 160.0, 161.3, 161.7, 171.0. MS (EI, 70 eV): 502 [M^+], Anal. Calcd. for $C_{24}H_{18}N_6O_5S$: C, 57.37; H, 3.61; N, 16.72. Found: C, 57.11; H, 3.83; N, 16.43.

4.14 | 4-(6-Amino-4-(benzo[*d*][1,3]dioxol-5-yl)-3,5-dicyano-2-oxopyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17e)

Yellow crystals (413 mg, 80%). Mp > 300°C. IR (KBr): ν_{max}/cm^{-1} 3363, 3315, 3206 (NH and NH_2), 2219 (C≡N), 1628 (CO), 1339, 1169 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 2.33 (s, 3H, CH_3), 6.16 (s, 1H, C*H*), 6.22 (s, 2H, OCH_2O), 7.02 to 7.13 (m, 3H, Ar*H*), 7.63 to 7.66 (d, J = 8.8 Hz, 1H, Ar*H*), 8.05 (br d, J = 8.8 Hz, 4H, Ar*H* and NH_2), 11.62 (s, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.1, 75.4, 95.5, 101.9, 108.5, 115.2, 115.7, 120.8, 122.6, 124.0, 128.0, 129.7, 138.0, 138.2, 148.6, 149.0, 156.9, 157.4, 159.2, 159.6, 170.5. MS (EI, 70 eV): 516 [M^+]. Anal. Calcd. for $C_{24}H_{16}N_6O_6S$: C, 55.81; H, 3.12; N, 16.27. Found: C, 55.57; H, 3.37; N, 16.56.

4.15 | 4-(6-Amino-3,5-dicyano-4-(4-nitrophenyl)-2-oxopyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (17f)

Brown crystals (362 mg, 70%). Mp > 300°C. IR (KBr): ν_{max}/cm^{-1} 3430, 3363, 3317 (NH and NH_2), 2220 (C≡N), 1642 (CO), 1348, 1173 (SO_2). ^1H NMR (400 MHz, DMSO-d_6): δ/ppm 2.33 (s, 3H, CH_3), 6.23 (s, 1H, C*H*), 7.64 to 7.67 (d, J = 8.8 Hz, 2H, Ar*H*), 7.83 to 7.85 (d, J = 8.8 Hz, 2H, Ar*H*), 8.05 to 8.08 (d, J = 8.8 Hz, 2H, Ar*H*), 8.22 (br., 2H, NH_2), 8.42 to 8.45 (d, J = 8.8 Hz, 2H, Ar*H*), 11.61 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ/ppm 12.1, 75.4, 95.5, 115.1, 115.7, 123.9, 129.0, 129.6, 130.0, 138.0, 140.9, 141.2, 148.6, 156.9, 157.3, 159.1, 159.6, 170.4. MS (EI, 70 ev): 517 [M^+]. Anal. Calcd. for $C_{23}H_{15}N_7O_8S$: C, 53.38; H, 2.92; N, 18.95. Found: C, 53.09; H, 2.59; N, 19.16.

ACKNOWLEDGMENTS

Ismail A. Abdelhamid and Amr M. Abdelmoniem acknowledge Alexander von Humboldt foundation for research fellowships.

ORCID

Amr M. Abdelmoniem https://orcid.org/0000-0002-9243-7589
Ismail A. Abdelhamid https://orcid.org/0000-0003-1220-8370

REFERENCES AND NOTES

[1] G. G. Zhanel, J. A. Karlowsky, G. K. Harding, A. Carrie, T. Mazzulli, D. E. Low, D. J. Hoban, D. J. Hoban, *Antimicrob. Agents Chemother.* **2000**, *44*, 1089.

[2] J. C. Underwood, R. W. Harvey, D. W. Metge, D. A. Repert, L. K. Baumgartner, R. L. Smith, T. M. Roane, L. B. Barber, *Environ. Sci. Technol.* **2011**, *45*, 3096.

[3] J. Zander, S. Besier, S. Faetke, S. H. Saum, V. Müller, T. A. Wichelhaus, *Int. J. Antimicrob. Agents* **2010**, *36*, 562.

[4] J. S. M. Tondolo, E. S. Loreto, F. P. K. Jesus, V. Dutra, L. Nakazato, S. H. Alves, J. M. Santurio, *Antimicrob. Agents Chemother.* **2018**, *62*, e01685.

[5] S. Hida, M. Yoshida, I. Nakabayashi, N. N. Miura, Y. Adachi, N. Ohno, *Biol. Pharm. Bull.* **2005**, *28*, 773.

[6] R. Gupta, I. Kazmi, M. Afzal, R. Khan, M. Chauhan, F. A. Al-Abbasi, A. Ahmad, F. Anwar, *Mol. Cell. Biochem.* **2013**, *384*, 279.

[7] M. M. Ghorab, F. A. Ragab, M. M. Hamed, *Eur. J. Med. Chem.* **2009**, *44*, 4211.

[8] R. Raz, B. Chazan, Y. Kennes, R. Colodner, E. Rottensterich, M. Dan, I. Lavi, W. Stamm, *Clin. Infect. Dis.* **2002**, *34*, 1165.

[9] A. Kolocouris, K. Dimas, C. Pannecouque, M. Witvrouw, G. B. Foscolos, G. Stamatiou, G. Fytas, G. Zoidis, N. Kolocouris, G. Andrei, R. Snoeck, E. De Clercq, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 723.

[10] J. Quintela, C. Peinador, L. Botana, M. Estévez, R. Riguera, *Bioorg. Med. Chem.* **1997**, *5*, 1543.

[11] A. S. Girgis, H. M. Hosni, I. S. Ahmed-Farag, *Zeitschrift Für Naturforsch. B* **2003**, *58*, 678.

[12] A.-G. E. Amr, M. M. Abdulla, *Bioorg. Med. Chem.* **2006**, *14*, 4341.

[13] J.-K. Son, L.-X. Zhao, A. Basnet, P. Thapa, R. Karki, Y. Na, Y. Jahng, T. C. Jeong, B.-S. Jeong, C.-S. Lee, E.-S. Lee, *Eur. J. Med. Chem.* **2008**, *43*, 675.

[14] E. Carosati, R. Mannhold, P. Wahl, J. B. Hansen, T. Fremming, I. Zamora, G. Cianchetta, M. Baroni, *J. Med. Chem.* **2007**, *50*, 2117.

[15] A. A. Joshi, C. L. Viswanathan, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613.

[16] N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, J. T. Leonard, *Biol. Pharm. Bull.* **2004**, *27*, 1683.

[17] P. Narender, U. Srinivas, M. Ravinder, B. A. Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U. S. N. Murthy, V. J. Rao, *Bioorg. Med. Chem.* **2006**, *14*, 4600.

[18] R. G. Ridley, *Nature* **2002**, *415*, 686.

[19] A. Tsotinis, M. Vlachou, S. Zouroudis, A. Jeney, F. Timár, D. E. Thurston, C. Roussakis, *Lett. Drug Des. Discov.* **2005**, *2*, 189.

[20] A. K. Agrawal, S. A. Jenekhe, *Chem. Mater.* **1993**, *5*, 633.

[21] G. Jégou, S. A. Jenekhe, *Macromolecules* **2001**, *34*, 7926.

[22] S. A. Jenekhe, *Science* (80-.) **1999**, *283*, 372.

[23] S. I. Alqasoumi, A. M. Al-Taweel, A. M. Alafeefy, M. M. Hamed, E. Noaman, M. M. Ghorab, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6939.

[24] M. S. Al-Said, M. M. Ghorab, M. S. Al-Dosari, M. M. Hamed, *Eur. J. Med. Chem.* **2011**, *46*, 201.

[25] M. G. Gündüz, G. Sevim Öztürk, İ. M. Vural, R. Şimşek, Y. Sarıoğlu, C. Şafak, *Eur. J. Med. Chem.* **2008**, *43*, 562.

[26] R. León, C. de los Ríos, J. Marco-Contelles, O. Huertas, X. Barril, F. Javier Luque, M. G. López, A. G. García, M. Villarroya, *Bioorg. Med. Chem.* **2008**, *16*, 7759.

[27] R. Miri, K. Javidnia, H. Mirkhani, B. Hemmateenejad, Z. Sepeher, M. Zalpour, T. Behzad, M. Khoshneviszadeh, N. Edraki, A. R. Mehdipour, *Chem. Biol. Drug Des.* **2007**, *70*, 329.

[28] O. I. El-Sabbagh, M. A. Shabaan, H. H. Kadry, E. S. Al-Din, *Arch. Der Pharm. Weinheim Ger.* **2010**, *343*, 519.

[29] Y. Sawada, H. Kayakiri, Y. Abe, T. Mizutani, N. Inamura, M. Asano, C. Hatori, I. Aramori, T. Oku, H. Tanaka, *J. Med. Chem.* **2004**, *47*, 2853.

[30] R. Shan, C. Velazquez, E. E. Knaus, *J. Med. Chem.* **2004**, *47*, 254.

[31] I. A. Abdelhamid, *Synlett* **2009**, *2009*, 625.

[32] S. A. S. Ghozlan, M. H. Mohamed, A. M. Abdelmoniem, I. A. Abdelhamid, *ARKIVOC* **2009**, x, 302.

[33] A. M. Abdelmoniem, M. A. Ramadan, S. A. S. Ghozlan, I. A. Abdelhamid, *J. Heterocyclic Chem.* **2017**, *54*, 1193.

[34] S. A. S. Ghozlan, D. M. Abdelmoniem, M. F. Mady, A. M. Abdelmoniem, I. A. Abdelhamid, *Heterocycles* **2016**, *92*, 637.

[35] S. A. S. Ghozlan, A. G. Ahmed, I. A. Abdelhamid, *J. Heterocyclic Chem.* **2016**, *53*, 817.

[36] M. M. Abdelkhalik, I. A. Abdelhamid, M. H. Elnagdi, *Synlett* **2007**, 2979.

[37] N. A. Al-Awadi, I. A. Abdelhamid, A. M. Al-Etaibi, M. H. Elnagdi, *Synlett* **2007**, *2007*, 2205.

[38] I. A. Abdelhamid, M. H. Mohamed, A. M. Abdelmoniem, S. A. S. Ghozlan, *Tetrahedron* **2009**, *65*, 10069.

[39] S. K. Salama, M. F. Mohamed, A. F. Darweesh, A. H. M. Elwahy, I. A. Abdelhamid, *Bioorg. Chem.* **2017**, *71*, 19.

[40] A. M. Abdelmoniem, S. A. S. Ghozlan, H. Butenschön, I. A. Abdelhamid, *Eur. J. Chem.* **2016**, *7*, 73.

[41] A. M. Abdella, A. H. M. Elwahy, I. A. Abdelhamid, *Curr. Org. Synth.* **2016**, *13*, 601.

[42] S. K. Salama, A. F. Darweesh, I. A. Abdelhamid, A. H. M. Elwahy, *J. Heterocyclic Chem.* **2017**, *54*, 305.

[43] S. A. S. Ghozlan, M. A. Ramadan, A. M. Abdelmoniem, A. H. M. Elwahy, I. A. Abdelhamid, J. Turkish, *Chem* **2017**, *41*, 410.

[44] S. A. S. Ghozlan, D. M. Abdelmoniem, A. M. Abdelmoniem, I. A. Abdelhamid, J. Turkish, *Chem* **2016**, *40*, 434.

[45] S. A. S. Ghozlan, M. A. Ramadan, A. M. Abdelmoniem, I. A. Abdelhamid, *Heterocycles* **2016**, *92*, 1075.

[46] S. A. S. Ghozlan, M. F. Mohamed, A. G. Ahmed, S. A. Shouman, Y. M. Attia, I. A. Abdelhamid, *Arch. Pharm. (Weinheim)* **2015**, *348*, 113.

[47] Z. Karimi-jaberi, Z. Takmilifard, *Eur. Chem. Bul.* **2013**, *2*, 211.

[48] M. F. Mohamed, Y. M. Attia, S. A. Shouman, I. A. Abdelhamid, *Anticancer Agents Med Chem.* **2017**, *17*, 1084.

[49] A. M. Abdelmoniem, T. A. Salaheldin, I. A. Abdelhamid, A. H. M. Elwahy, *J. Heterocyclic Chem.* **2017**, *54*, 2670.

[50] S. A. S. Ghozlan, M. A. Ramadan, A. M. Abdelmoniem, I. A. Abdelhamid, *ARKIVOC* **2019**, 30.

[51] E. S. Darwish, K. A. Atia, A. M. Farag, *Heterocycles* **2014**, *89*, 1393.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Abdelmoniem AM, Abdelrahman MGM, Ghozlan SAS, Abdelhamid IA. Synthesis of novel hexahydroquinolines and 6-amino-2-oxopyridine-3,5-dicarbonitriles incorporating sulfamethoxazole via [3 + 3] annulation. *J Heterocyclic Chem*. 2019;1–9. https://doi.org/10.1002/jhet.3737