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Synthesis of novel 5-amino-1,3,4-thiadiazole-2-sulfonamide containing acridine sulfonamide/carboxamide compounds and investigation of their inhibition effects on human carbonic anhydrase I, II, IV and VII

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ABSTRACT

Herein, we report that acridine intermediates **5** were obtained from the reduction of nitro acridine derivatives **4**, which were synthesized via condensation of dimedone, *p*-nitrobenzaldehyde with 4-amino-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)benzamide, respectively. Then acridine sulfonamide/carboxamide (**7a–i**) compounds were synthesized by reaction of amino acridine **5** with sulfonyl chlorides and carbamoyl chlorides. The new compounds were characterized by melting points, FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS analyzes. The evaluation of in vitro test of the synthesized compounds against hCA I, II, IV and VII showed that some of them are potent inhibitors. Among them, compound **7e** showed the most potent activity against hCA II with a K_I of 7.9 nM.

1. Introduction

Nitrogen containing heterocyclic systems are underlined by their key role as intermediates of natural products. As important subunits, acridines are in use as building block for heterocyclic systems and have a strong influence on biological, pharmaceutical, and material sciences. Acridine scaffold has been extensively used in medicinal chemistry providing many highly-substituted acridines with biological properties, such as anti-oxidant [1], anti-glaucoma [2], anti-Alzheimer [3], anti-antifungal [4], anti-bacterial [5], anti-microbial [4,6], anti-malarial [7], anti-cancer [8], anti-tubercular [9], anti-diabetic [10], and anti-viral [7b] agents. Moreover, they are well known as photo sensitizer in organic dye laser applications in florescence chemistry [11], and their derivatives are widely applied as intercalator agent on DNA [12].

Carbonic anhydrases are metalloenzymes responsible for the reversible hydration of carbon dioxide to bicarbonate. In human, different CA isoforms (up to now 16 isoforms have been described in higher vertebrates) participate in many physiological reactions in different cellular and organ/tissue localization such as regulation of respiration, bone resorption, pH regulation and CO_2 homeostasis, and tumorigenicity [13,14]. Since late 40s different CA isoforms are preferred as drug targets due to not only their different cellular localization and organ/tissue distribution but also diversity of physiological reactions they involve in.

An important class of CA inhibitors (CAIs), is represented by sulfonamides and their isoesters (sulfamides, sulfamates), such as pediazole, acetohexamide, sulfadiazine, topiramate, mafenide [15] which have been in clinical use as drugs for decades. They possess various biological activities such as antibacterial [16], anti-cancer [17], carbonic anhydrase inhibitor for glaucoma treatment [18,19], acetylcholinesterase inhibitor agents for Alzheimer's disease [20], antiobesity [21], and high-ceiling diuretic [22].

Herein we report the synthesis and the inhibition profiles against hCA I, II, IV and VII, for a small series of acridines incorporated with 4-amino-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) benzamide.

2. Material and methods

2.1. Materials and instrumentation

The chemicals used in the synthesis of 5-amino-1,3,4-thiadia zole-2-sulfonamide based acridine compounds containing

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sulfonamide group and carboxamide derivatives were obtained from Merck and Aldrich Chemical Company. All chemicals and solvents used for the synthesis were of spectroscopic reagent grade. Melting points were measured on a Bibby Scientific Stuart Digital, Advanced, and SMP30. Fourier Transform Infrared (FT–IR) spectra were recorded on Perkin Elmer, Spectrum Two FT–IR spectrometer. Synthesis operations of all products were realized with CEM Discover–SP W/Activent Microwave Synthesis System. The ^{1}H NMR and ^{13}C NMR spectra were obtained in DMSO d_6 with Bruker Biospin Avance III as solvents with tetramethylsilane as the internal reference. The mass analyses were performed on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/HRMS at the advanced technology research center of Dumlupınar University (ILTEM).

*2.2. Procedure for preparation of synthesis of N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-4-(3,3,6,6-tetramethyl-9-(4-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl) benzamide compound (**4**)*

A mixture of a 5,5-dimethylcyclohexane-1,3-dione (**1**) (0.28 g, 2 mmol), 4-nitrobenzaldehyde (**2**) (0.15 g, 1 mmol) and 4-amino-*N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)benzamide (**3**) [23] (0.30 g, 1 mmol) in 5 mL ethanol was irradiated in a microwave synthesis system (200 W and at 100 °C) for 10 min. The progress of the reaction was monitored by TLC. Once the reaction is completed, the mixture was cooled to room temperature and solid filtered off and washed with H_2O. The acridine compound containing nitro derivative (**4**) were purified and recrystallized from the ethanol (92%) [24].

*2.2.1. N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-4-(3,3,6,6-tetramethyl-9-(4-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6, 7,8-octahydroacridin-10 (9H)-yl)benzamide compound (**4**)*

As yellow crystal, (0.622 g, 92%), mp. 280–282 °C. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 0.75 (s, 6H, 2x —CH_3), 0.87 (s, 6H, 2x —CH_3), 1.81 (d, 2H, J = 17.40 Hz, —CH_2), 2.03 (d, 2H, J = 16.04 Hz, —CH_2), 2.21–2.28 (m, 4H, 2x —CH_2), 5.20 (s, ^{1}H, —CH), 7.63 (d, 2H, J = 8.70 Hz, Ar—H), 7.76 (d, 2H, J = 8.10 Hz, Ar—H), 8.16 (d, 2H, J = 8.70 Hz, Ar—H), 8.39 (d, 2H, J = 8.10 Hz, Ar—H), 8.41 (s, 2H, —SO_2NH_2), 13.60–13.80 (br, ^{1}H, —NH); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm): 26.61, 29.59, 32.54, 33.46, 41.46, 49.86, 112.61, 123.77, 129.52, 129.96, 130.83, 132.29, 142.81, 146.19, 150.94, 153.98, 162.60, 165.29, 165.33, 195.52; IR (cm^{-1}): 3387 (—NH), 3355 (—NH_2), 3026 (Ar—H), 1647 (C=O); HRMS (QTOF-ESI): m/z calcd. for $C_{32}H_{32}N_6O_7S_2$: 676.1774; found: 675.1818 $[M-H]^-$.

*2.3. General procedure for preparation of synthesis of 4-(9-(4-aminophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)-N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) benzamide compound (**5**)*

$Na_2S{\cdot}9H_2O$ (1 mmol) and sulfur (2 mmol) were dissolved by boiling in 10 mL of water. This solution (sodium polysulfur) was then added dropwise to a stirred solution of warm *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-4-(3,3,6,6-tetramethyl-9-(4-nitrophenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10 (9*H*)-yl) benzamide compound (**4**) (0.68 g, 1 mmol) in ethanol-water. The progress of the reaction was monitored by TLC. Once the reaction was completed, the mixture was cooled to room temperature, filtered and the filtrate solid filtered off and washed with H_2O. The novel amino-acridine sulfonamide product was purified and recrystallized from chloroform (76%) [2b].

*2.3.1. 4-(9-(4-Aminophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)-N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) benzamide (**5**)*

As yellow crystal, (0.491 g, 76%), mp. 270–272 °C. ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 0.71 (s, 6H, 2x — CH_3), 0.93 (s, 6H, 2x —CH_3), 1.78 (d, 2H, J = 17.51 Hz, —CH_2), 1.95 (s, 2H, —NH_2), 2.00 (d, 2H, J = 15.91 Hz, —CH_2), 2.16–2.28 (m, 4H, 2x —CH_2), 4.90 (s, ^{1}H, —CH), 6.45 (d, 2H, J = 8.20 Hz, Ar—H), 6.98 (d, 2H, J = 8.17 Hz, Ar—H), 7.44–7.51 (m, 4H, Ar—H), 8.40 (s, 2H, —SO_2NH_2), 13.60–13.80 (br, ^{1}H, —NH); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm): 26.53, 29.79, 31.04, 32.45, 41.39, 50.19, 114.12, 114.25, 128.41, 130.32, 131.41, 134.52, 134.69, 141.02, 142.86, 146.82, 149.67, 149.98, 167.03, 195.64; IR (cm^{-1}): 3391 (—NH), 3361 (—NH_2), 3031 (Ar—H), 2986 (C—H), 1656 (C=O); HRMS (QTOF-ESI): m/z calcd. for $C_{32}H_{34}N_6O_5S_2$: 646.2032; found: 645.1956 $[M-H]^-$.

*2.4. General procedure for preparation of synthesis of 5-amino-1,3,4-thiadiazole-2-sulfonamide containing acridine sulfonamide/carboxamide compounds (**7a–i**)*

4-(9-(4-Aminophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9*H*)-yl)-*N*-(5-sulfamoyl-1,3,4-thiadia zol-2-yl)benzamide derivative (**5**) (0.64 g, 1 mmol) and sulfonyl/-carboxyl chlorides (**6a–i**) (1 mmol) were stirred in 5 mL dry pyridine for 2 h at room temperature. Then, the solvent was removed under *vacuo* and washed with H_2O and the crude product was purified by recrystallization from chloroform (65–95%).

*2.4.1.N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-4-(3,3,6,6-tetramethyl-1,8-dioxo-9-(4-(phenylsulfonamido) phenyl)-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzamide (**7a**)*

As yellow crystal, (0.715 g, 91%), mp. 311–313 °C ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 0.73 (s, 6H, 2x — CH_3), 0.95 (s, 6H, 2x —CH_3), 1.75 (d, 2H, J = 17.28 Hz, —CH_2), 1.99 (d, 2H, J = 15.89 Hz, —CH_2), 2.15–2.22 (m, 4H, 2x —CH_2), 4.93 (s, ^{1}H, —CH), 6.97 (d, 2H, J = 8.51 Hz, Ar—H), 7.18 (d, 2H, J = 8.51 Hz, Ar—H), 7.47–7.70 (m, 7H, Ar—H), 8.35 (d, 2H, J = 8.59 Hz, Ar—H), 8.38 (s, 2H, —SO_2-NH_2), 10.20 (s, ^{1}H, —NH), 12.80–13.60 (br, ^{1}H, —NH); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm): 26.45, 29.68, 31.77, 32.49, 41.41, 49.99, 113.46, 120.63, 126.97, 128.56, 128.64, 129.55, 130.77, 133.21, 135.73, 140.16, 142.62, 142.66, 142.91, 150.15, 150.25, 165.16, 165.53, 195.51; IR (cm^{-1}): 3384 (—NH), 3357 (—NH_2), 3021 (Ar—H), 2982 (C—H), 1654 (C=O); HRMS (QTOF-ESI): m/z calcd. for $C_{38}H_{38}N_6O_7S_3$: 786.1964; found: 785.2004 $[M-H]^-$.

*2.4.2. N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-4-(3,3,6,6-tetramethyl-9-(4-(4-methylphenylsulfonamido) phenyl)-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9H)-yl)benzamide (**7b**)*

As yellow crystal, (0.752 g, 94%), mp. 319–321 °C ^{1}H NMR (400 MHz, DMSO d_6) δ (ppm): 0.70 (s, 6H, 2x — CH_3), 0.90 (s, 6H, 2x —CH_3), 1.75 (d, 2H, J = 17.25 Hz, —CH_2), 1.99 (d, 2H, J = 15.85 Hz, —CH_2), 2.15–2.21 (m, 4H, 2x —CH_2), 2.30 (s, 3H, —CH_3), 4.95 (s, ^{1}H, —CH), 6.97 (d, 2H, J = 8.43 Hz, Ar—H), 7.17 (d, 2H, J = 8.43 Hz, Ar—H), 7.28 (d, 2H, J = 8.23 Hz, Ar—H), 7.59 (d, 2H, J = 8.23 Hz, Ar—H), 7.66 (d, 2H, J = 8.50 Hz, Ar—H), 8.35 (d, 2H, J = 8.50 Hz, Ar—H), 8.40 (s, 2H, —SO_2NH_2), 10.10 (s, ^{1}H, —NH), 13.40–13:70 (br, ^{1}H, —NH); ^{13}C NMR (100 MHz, DMSO d_6) δ (ppm): 21.41, 26.44, 29.66, 31.77, 32.49, 41.42, 49.99, 113.42, 113.48, 120.36, 127.03, 128.54, 128.64, 130.01, 130.79, 135.88, 137.37, 142.43, 142.99, 143.53, 150.13, 150.26, 165.29, 165.40, 195.53; IR (cm^{-1}): 3387 (—NH), 3365 (—NH_2), 3027 (Ar—H), 2975 (C—H), 1658 (C=O); HRMS (QTOF-ESI): m/z calcd. for $C_{39}H_{40}N_6O_7S_3$: 800.2121; found: 799.2164 $[M-H]^-$.