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New aminobenzenesulfonamide–thiourea conjugates: Synthesis and carbonic anhydrase inhibition and docking studies

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ABSTRACT

A variety of 1-substituted-3-(3-aminosulfonylphenyl)thioureas (**3a**–**k**) and two new 1-aroyl-3-(4-aminosulfonylphenyl)thiourea derivatives (**5a** and **5b**) were synthesized by reaction of 3-aminobenzenesulfonamide and 4-aminobenzenesulfonamide respectively with freshly prepared aroyl/heteroaryl isothiocyanates in dry acetonitrile. FTIR, ^{1}H NMR, ^{13}C NMR, GC–MS and elemental analyses data confirmed the assigned structures to the synthesized compounds. Further structure of compound (**3g**) was also confirmed by single crystal XRD analysis. The compounds were investigated as inhibitors of the bovine erythrocyte carbonic anhydrase isoform II (bCA II). The inhibition constants of these compounds against bCA II were in the range 0.011–17.1 μM. Among the evaluated compounds, 1-substituted -3-(3-aminosulfonylphenyl)thiourea derivatives **3h** and **5a** were the most potent inhibitors with IC_{50} of 0.052 and 0.011 μM, respectively. *In silico* docking and molecular dynamics simulation studies were performed against bCA II and human CA II enzymes to rationalize the inhibitory properties of these compounds.

1. Introduction

The zinc metallo-enzyme carbonic anhydrase (CA, EC 4.2.1.1) catalyzes the rapid reversible conversion of carbon dioxide and water into a proton and the bicarbonate ion [1–3]. Carbonic anhydrases are involved in crucial physiological processes connected with transport of CO_2/bicarbonate, homeostasis, electrolyte secretion in a variety of tissues/organs, biosynthetic reactions (such as gluconeogenesis, ureagenesis and lipogenesis), respiration, calcification, tumorigenicity, and bone resorption [1–7]. Deficiency of carbonic anhydrase II is the leading defect in the syndrome of osteoporosis, cerebral calcification and renal tubular acidosis [8]. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, most likely by slowing the formation of bicarbonate ions with consequent decrease in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP). Acetazolamide is a well-known example of clinically established carbonic anhydrase inhibitor [9]. Sulfonylureas are amongst the most familiar sulfonamide derivatives possessing potent hypoglycemic activity due to their ability to stimulate the release of insulin from the pancreatic islets. Carbutamide, tolbutamide, chlorpropamide and tolazamide belong to the first generation of sulfonylureas while second generation include glyburide and glipizide [10–12]. Sulfonamides are well known for their diuretic [13], anti-carbonic anhydrase [14] and antimalarial activity [15–17].

Among the broad spectrum of activities exhibited by sulfonamides, their role as inhibitors of the zinc containing metalloenzyme carbonic anhydrase (CA) is presumably most widely studied. Many sulfonamide CA inhibitors have been used as therapeutic agents against various diseases including glaucoma, gastroduodenal ulcers, acid–base disequilibria, and various neurological disorders [18–21].

Thus 4-(3,4-dichloro-phenylureido)thioureido-benzene sulfonamide possessing a thiourea scaffold is an effective *in vitro* inhibitor of carbonic anhydrase; inhibited the *ex vivo* growth of *Plasmodium falciparum* [22]. Several antiplasmodial 7-chloro-4-aminoquinolyl-

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derived sulfonamides, ureas, thioureas and amides have been synthesized and tested against chloroquine-resistant (CQR) and chloroquine susceptible (CQS) *P. falciparum* [23].

Previously we have shown sulfanilamide–thiourea hybrids to be effective antimicrobial agents and urease inhibitors [24]. Herein we report synthesis of isomeric 3-aminobenzenesulfonamide appended to thiourea nucleus and their comparison with 4-aminobenzenesulfonamide derivatives. In the present work, we have expanded this new class of inhibitors by synthesizing novel 1-substituted-3-(3-aminosulfonylphenyl)thioureas (**3a**–**k**) and two new 1-aroyl-3-(4-aminosulfonylphenyl)thiourea derivatives (**5a** and **5b**) and determined their inhibition activity against bCA II. Some of the structurally related sulfonamides reported in literature are presented in Fig. 1.

2. Results and discussion

2.1. Chemistry

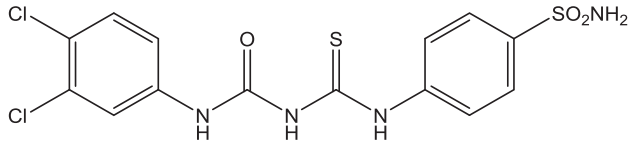
A variety of aroyl/heteroaryl isothiocyanates (**1a**–**k**) were prepared *in situ* by reaction of corresponding acid chlorides with an equimolar quantity of potassium thiocyanate in dry acetonitrile. Treatment of isothiocyanates with 3-aminobenzenesulfonamide (**2**) in dry acetonitrile in 1:1 M ratio furnished corresponding 1-aroyl/heteroaryl 3-(3-aminosulfonylphenyl)thioureas (**3a**–**k**) in 80–91% yield (Scheme 1). Two new 1-aroyl-3-(4-aminosulfonylphenyl) thioureas **5a** and **5b** were similarly synthesized by reaction of thiophene-2-carbonyl isothiocyanate and coumarin-3-carbonyl isothiocyanate respectively with 4-aminobenzenesulfonamide (**4**) (Scheme 2).

FTIR spectra of the aroyl/heteroaryl substituted thioureas **3a**–**k** and **4a**–**b** were in accordance with those reported for similar compounds [25–27]. In ^{1}H NMR spectra the characteristic singlets for N_1 and N_3 protons were found in a relatively wide range of δ 8.1–9.1 and 10.8–12.1 respectively. The typical differences in the aromatic region of 3-amino and 4-aminobenzenesulfonamides were also noted. Thus, in case of 4-amino compounds (**5a**,**b**) two doublets are observed around 7.81 and 7.90 for aromatic protons, while 3-aminobenzenesulfonamide derivatives (**3a**–**k**), display three to four different signals due to nearly all unequivalent aromatic protons.

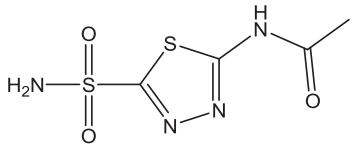
Fig. 2 shows the molecular structure of 1-(2-furanyl)-3-(3-aminosulfonylphenyl) thiourea (**3g**) and Table 1 summarizes the main geometric parameters. The furanyl-thiourea moiety is almost planar with a torsion angle O2–C5–C4–C3 of 5.5(3)°. Thiourea torsion angles are O2–C5–N1–C6 1.1(3)°and N2–C6–N1–C5 −1.3(3)°. An intramolecular N2–H…O2 hydrogen bond is connected with that conformation. The furanyl and phenyl rings make a dihedral angle of 22.3(1)°. Other geometric parameters lie in expected ranges. Somewhat related molecular structures are MUWCUD [28] or FAQPOE [29], both with the aminosulfonyl group in para-position and *p*-tolyl or trimethoxyphenyl instead of the furanyl group, respectively. The crystal packing of (**3g**) (Fig. 3) shows intermolecular N1–H…S1 ($-x + 1, -y, -z$) and N3–H31…O4 ($x, -y + 0.5, z-0.5$) interactions that link molecules into pairs of centrosymmetric dimers that are stacked along [001].

2.2. Carbonic anhydrase inhibition

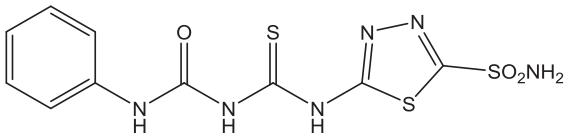
All synthesized compounds were tested for their ability to act as carbonic anhydrase (CA) inhibitors against bovine CA II (bCA-II) isozyme. CA inhibition data for these compounds is given in Table 2. CA inhibitory activities of these compounds were investigated against the standard clinically used inhibitor acetazolamide. The compounds **3a**–**3c** differ only in the relative position of the chloro group on the 3-(3-aminosulfonylphenyl)thioureas ring, have shown IC_{50} values 13.5 ± 1.40, 0.22 ± 0.02 and 5.64 ± 0.09 μM, respectively. Among these chloro group substitution at position 3



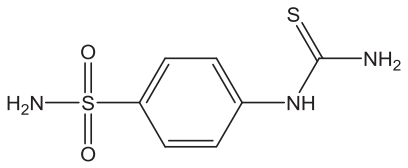
1-(3,4-dichlorophenylcarbamoyl)-3-(4-aminosulfonylphenyl) thiourea



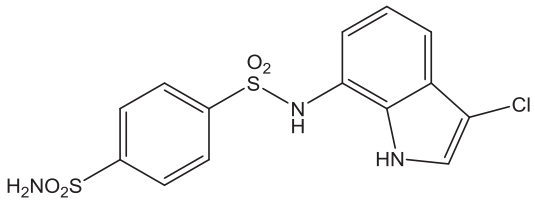
Acetazolamide



1-(4-1-(3,4-dichlorophenylcarbamoyl)-3-(4-aminosulfonylphenyl) thioureasulphonylaminophenyl)thiourea



1-(4-aminosulfonylphenyl)thiourea



N-(3-chloro-1*H*-indol-7-yl)benzene-1,4-disulfonamide

Fig. 1. Structures of some pharmacologically important related compounds reported in literature.