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Palladium-catalyzed amination of 2-chlorothienopyridone with primary aromatic amines

Samir A. Al-Taweel^{1*}, Salah A. Al-Trawneh¹ and Wal'A M. Al-Trawneh¹

Abstract: A series of ethyl 7-cyclopropyl-2-(arylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate (**9a-d**) were prepared by coupling of ethyl 7-cyclopropyl-2-chloro-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate (**8**) with primary aromatic amines via palladium-catalyzed amination using palladium acetate Pd(OAc)₂ in the presence of cesium fluoride in good yields. The new compounds were characterized by ¹H-NMR, ¹³C-NMR, mass spectrometry, high resolution mass spectrometry and elemental analysis. 7-cyclopropyl-2-(phenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**10a**) showed weak activity against *E.aerogenas* and *S.aureus* bacteria.

Subjects: Biochemistry; Microbiology; Pharmaceutical Science; Pharmacology

Keywords: 2-chloro-3-nitro-4-oxo-4; 7-dihydrothieno[2,3-*b*]pyridines; palladium catalyzed amination; primary aromatic amines; antibacterial activity

1. Introduction

The quinolones are synthetic antibiotics, which trace their origin to a concerted effort by scientists to synthesis novel antibacterial agents. After the discovery of nalidixic acid (**1**) (Figure 1) by Leshner in 1962 (Leshner, Froelich, Gruett, Bailey, & Brundage, 1962), an antibacterial agent, which is indicated for the treatment of urinary tract infection, the research in this area became more

ABOUT THE AUTHORS



Samir A. Al-Taweel

Samir A. Al-Taweel, the corresponding author, is working as Professor in Mutah University, Karak, Jordan. He has published more than 35 research papers in peer-reviewed international journals. He has guided ten MS students. The main focus of our research group is to develop simple and efficient synthetic strategies for the synthesis of new bioactive organic thiophene-based heterocyclic compounds. Recently, our research group interested in synthesizing dye-sensitizers, for the solar cell applications.

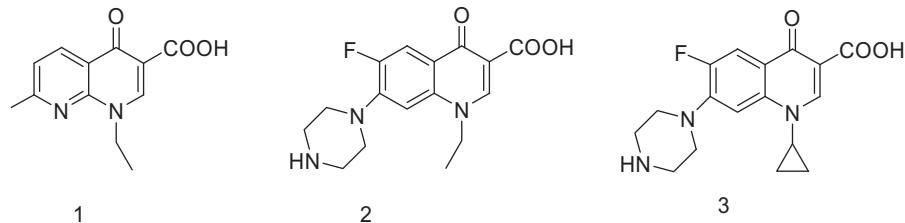
Salah A. Al-Trawneh is the co-author he is the associated professor in organic chemistry, the main interest of our research group is to develop simple and efficient synthetic protocol for the synthesis of new bioactive heterocyclic organic compounds.

Wal'A M. Al-Trawneh is a Master student conducting the synthesis and purification of the coupling products.

PUBLIC INTEREST STATEMENT

Antibiotic resistance is one of the biggest threats to global health, which is rising to alarming levels. The current research is the successful addition to the field of medicinal chemistry, in order to synthesize a new generation of antibiotics, which is bioisosters of fluoroquinolones antibiotics.

Figure 1. Structures of nalidixic acid, norfloxacin, and ciprofloxacin.



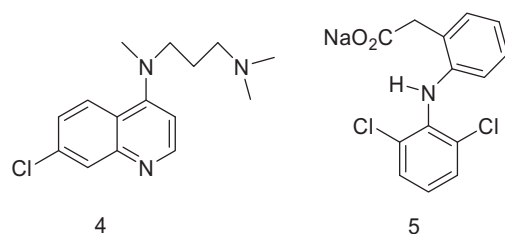
extensive. Fluoroquinolones are direct inhibitors of bacterial DNA synthesis (Dilica & Zhao, 1997). Fluoroquinolones inhibit two bacterial enzymes, DNA gyrase and topoisomerase IV, which have a distinct role in DNA replication. They bind to the complex of each of these enzymes with DNA, the resulting complexes, including the drug, block progress of the DNA replication enzyme complex. This results in damage to bacterial DNA and bacterial cell death.

Structure–activity relationship studies established that the following structural requirements are essential for the activity of fluoroquinolone: an amino group at C7, a small group such as methyl, ethyl or cyclopropyl at N1 and carboxylic acid group at C3, fluorine atom at C6 increases antibacterial activity, while piperazine moiety at C7 confers antipseudomonal properties. This research resulted in the discovery of the first fluoroquinolone, norfloxacin (2) (Figure 1) (Bryskier, 2005; Dalhoff & Schmitz, 2003; De Souza, 2005; Emami, Shafiee, & Foroumadi, 2006; Gootz & Brighty, 198; Peterson, 2001; Wagman & Wentland, 2007), which is characterized by a piperazine moiety at C7 and the most active fluoroquinolone, ciprofloxacin (3) (Figure 1) (Itoh et al., 1980; Koga, Itoh, Murayama, Suzue, & Irikura, 1980). The structure–activity relationship of quinolones has been the subject of extensive reviews (Felmingham et al., 1985; Maurer & Grohe, 1986; Petersen et al., 1996; Wise, Andrews, & Edwards, 1983).

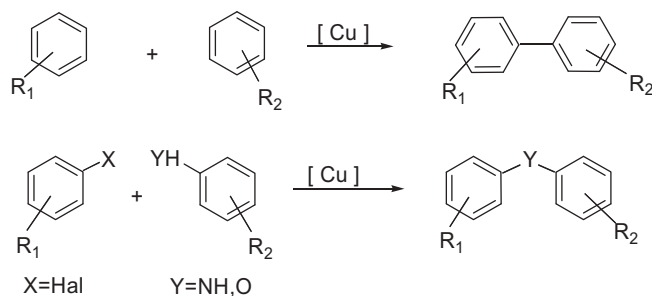
The synthesis of aromatic amines has attracted much attention due to their role in many fields of science and industry. They are common motifs in natural products, pharmaceuticals, agrochemicals, dyes and polymers. An aryl–nitrogen linkage is included in molecules like chloroquine (4) (Figure 2) (Johnson & Buell, 1952), a widely used antimalarial drug and dichlophenac (5) (Figure 2) (Skoutakis et al., 1988), a 5HT receptor antagonist. Dichlophenac (sodium[(2-[(2,6-dichlorophenyl)amino]phenyl)acetate]), is a potent NSAID (nonsteroidal anti-inflammatory drug), therapeutically used in inflammatory and painful diseases of rheumatic and nonrheumatic origin.

Despite the simplicity of arylamine moiety, the synthesis of these molecules is often difficult and challenging. This class of compounds was prepared via classical copper-mediated Ullmann coupling (Scheme 1) (Ullmann, 1903) and recently developed palladium-catalyzed aryl coupling (Schemes 2 and 3) (Hamann & Hartwig, 1998; Old, Wolfe, & Buchwald, 1998) are the more commonly used methods. The Ullmann coupling often requires high temperature and the use of copper salts in greater than stoichiometric amounts. The reaction is also very sensitive to the substitution on the aryl halide. Due to these limitations, copper salts have been supplanted by palladium catalyst (Hamann & Hartwig, 1998; Old et al., 1998).

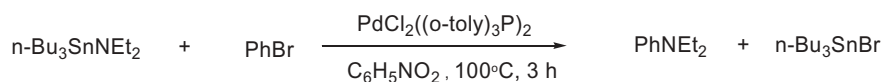
Figure 2. Structures of chloroquine(4) and diclophenac(5).



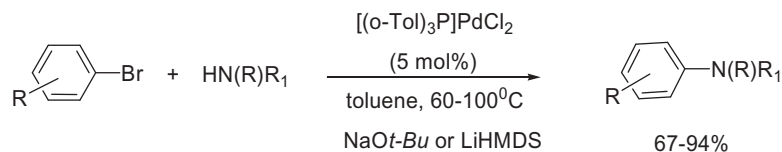
Scheme 1. Ullmann coupling.



Scheme 2. Migita palladium-catalyzed amination of aryl halides with aminotin compounds.



Scheme 3. Buchwald-Hartwig coupling.

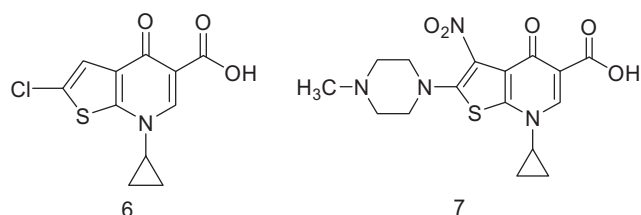


Palladium-catalyzed coupling of amines with aryl halides has become the most versatile tool for the preparation of aryl amines. This method has been introduced to provide an easy access to diarylamines. Migita and coworkers reported the first palladium-catalyzed amination of aryl halides in 1983 (Scheme 2) (Kosugi, Kameyama, & Migita, 1983). The treatment of bromobenzene with the aminotin compound in the presence of a palladium catalyst provided *N,N*-diethylaniline. However, this method requires the use of a stoichiometric quantity of a toxic and moisture sensitive tin reagent.

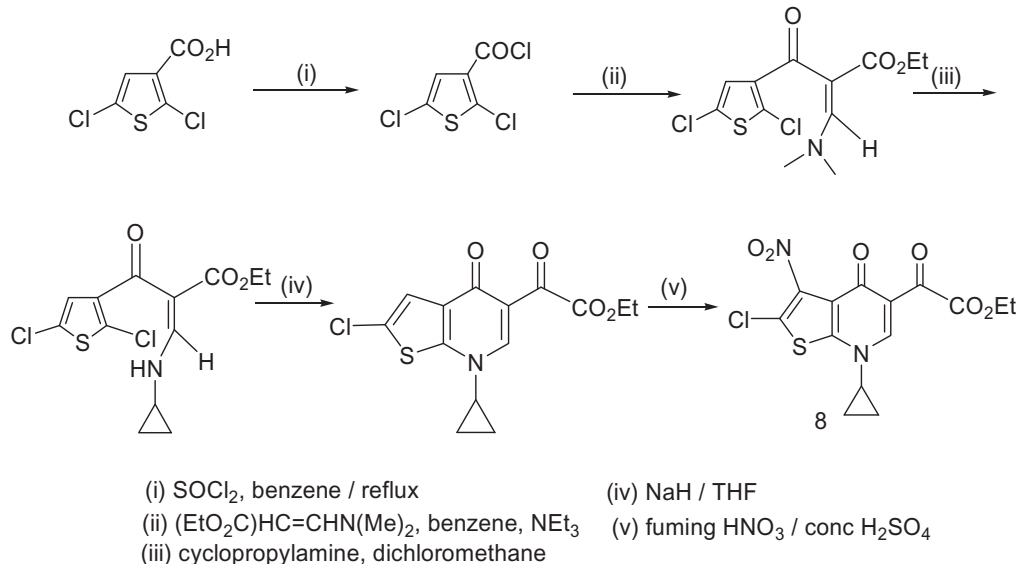
Buchwald, Guram, & Rennels (1995) and Hartwig and Lounie (1995) independently reported the palladium-catalyzed amination of aryl bromides with secondary amines using NaOtBu or LiHMDS as a base (Scheme 3) to afford tertiary arylamines in good to excellent yields. The palladium-catalyzed amination of aryl halides has been the subject of the extensive reviews (Hartwig, 1998; Wolfe, Wagaw, Marcoux, & Buchwald, 1998; Yang & Buchwald, 1999).

Several thienopyridones, namely;4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid, potential bioisosteres of quinolone antibacterial agents were prepared and bioassayed (Al-Masoudi, Al-Soud, & Al-Masoudi, 2000; Al-Trawneh et al., 2011; Bacon & Daun, 1991; Bompert, 1988; Bompert, Giral, Malicorne, & Puygrenier, 1987; Bravic, Cotrait, Bompert, & Giral, 1989; El-Abadelah et al., 1997; El-Abadelah, Sabri, & Al-Ashqar, 1997; El-Abadelah et al., 1998; Giral, Bompert, & Puygrenier, 1985; Hooper, Utsunomiya, & Hartwig, 2003; Yamazaki, Matsubara, Morishima, & Suenaga, 1983). 2-Chloro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acids (**6**) (Figure 3) has been prepared and was found to possess a good level of activity against gram-negative bacteria, while 7-Cyclopropyl-4,7-dihydro-2-(4-methyl-1-piperazinyl)-

Figure 3. Structures of some thieno[2,3-*b*]pyridine-5-carboxylic acids.



Scheme 4. Synthesis of ethyl 2-chloro-3-nitro-4-oxo-4,7-dihydro thieno[2,3-*b*]pyridine-5-carboxylate(8).



3-nitro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid(7) (Figure 3) showed reduced activity (El-Abadelah et al., 1998).

In view of the fact that most potent quinolones are substituted by different amino groups at C7 and since substitution at C2 and C3 positions of 4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid has not been sufficiently explored. This work involves the development of palladium-catalyzed amination of ethyl 2-chloro-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate(8) with primary aromatic amines to produce ethyl 7-cyclopropyl-2-(arylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate (9a-d, Scheme 7). Herein; their synthesis, characterization and biological activity are described.

2. Results and discussion

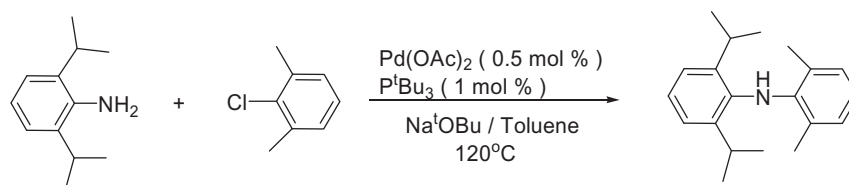
2.1. Synthesis

The title synthon (8), ethyl 2-chloro-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate, required in this work, is prepared from 2,5-dichlorothiophene-3-carboxylic acid, ethyl 3-(*N,N*-dimethylamino)acrylate and cyclopropyl amine by following the stepwise synthetic procedure reported in literature (Scheme 4). The overall yield of 8 starting from 2,5-dichlorothiophene-3-carboxylic acid is 40%. The latter compound, 2,5-dichlorothiophene-3-carboxylic acid was prepared by reaction of 3-acetyl-2,5-dichlorothiophene with Br_2/NaOH , following the literature procedure (El-Abadelah et al., 1997). Limited quantities of (8) have been prepared by this methodology, after sequential, meticulous and time-consuming steps.

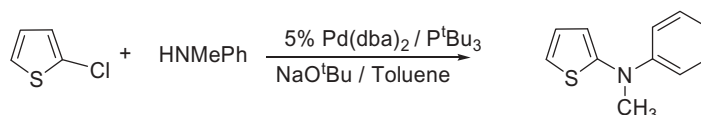
Attempt to bring about direct amination of 2-chloro substituent compound(8) by anisidine, in absence of $\text{Pd}(\text{OAc})_2$ (DMF at 120°C for 48 h) have, thus far, been unsuccessful, no coupled product (9a) have been isolated, as evidenced from $^1\text{H-NMR}$ analysis of the reaction mixture, and the recovery of the starting synthon (8) (70%).

While Ullmann reaction utilize copper for the formation of C-N bonds. Buchwald and Hartwig reported palladium-catalyzed amination of inactivated aryl bromides and aryl halides with low catalyst loading under mild conditions. Although, palladium is more expensive metal than copper, in addition to using sterically hindered, expensive phosphine ligands. Palladium-catalyzed amination of aryl halides has provided easy access to diarylamines. Bulky trialkylphosphines has been

Scheme 5. Palladium-catalyzed synthesis of diaryl amines.



Scheme 6. Palladium-catalyzed synthesis of 2-(N-methyl-N-phenylamino)thiophene.



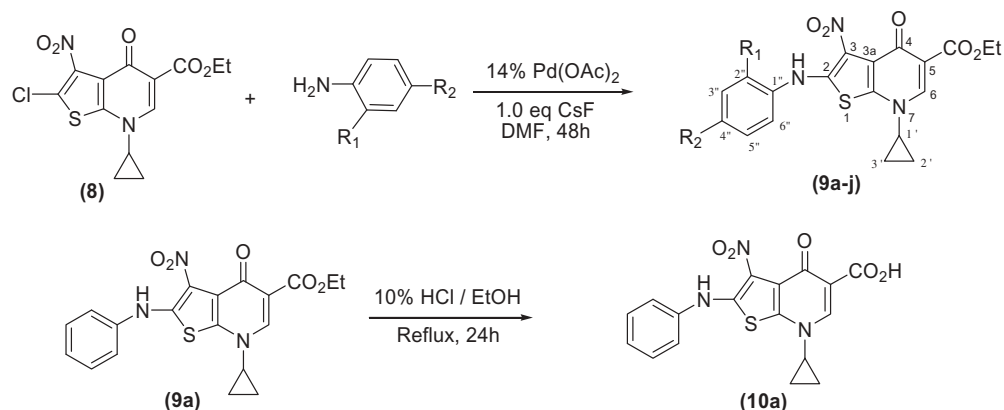
used for coupling of primary and secondary anilines (Wolfe, Hiroshi, Sadighi, Jingjun., & Buchwald, 2000) with inactivated, sterically hindered aryl chlorides (Scheme 5).

However, the application of Buchwald-Hartwig methodology to electron rich five-membered heteroaromatic substances, such as halo furans, thiophenes, pyrroles, indoles and imidazoles has been limited. Hartwig (Hooper et al., 2003) reported that bromothiophenes and chlorothiophenes react with diphenylamine and N-methylaniline in the presence of palladium catalyst using P^tBu_3 ligand (Scheme 6).

Preparation of the target, ethyl 7-cyclopropyl-2-(arylamino)-3-nitro-4-oxo-4,7-dihydro thieno [2,3-*b*]pyridine-5-carboxylate (**9a-d**) were carried out via palladium-catalyzed amination using $Pd(OAc)_2$ as a catalyst, with 14% loading, DMF as solvent and CsF as a base at 80°C for 48 h (Scheme 7). The cross-coupling products (**9a-d**), were isolated in 60–68% yield.

It is worth to mention that no cross amination products were isolated using potassium *t*-butoxide or calcium carbonate as bases. On the other hand, $Pd(OAc)_2$ catalyzed amination of synthon (**8**) with *p*-chloroaniline, *p*-bromoaniline, *p*-trifluoromethylaniline and 2,4-difluoroaniline produces the cross products (**9e-h**) in trace amounts, while *p*-nitroaniline and *p*-aminobenzenesulfamide failed to give products (**9i-j**). These results can be explained based on the nucleophilicity of

Scheme 7. Palladium-catalyzed coupling of thienopyridone(8**) with aniline derivatives.**



| Product No | 9a | 9b | 9c | 9d | 9e | 9f | 9g | 9h | 9i | 9j |
|----------------|----|------------------|-------------------|----|--------|--------|------------------|--------|------------------|----------------------------------|
| R ₁ | -H | -H | -H | -H | -H | -H | -H | -F | -H | -H |
| R ₂ | -H | -CH ₃ | -OCH ₃ | -F | -Cl | -Br | -CF ₃ | -F | -NO ₂ | -SO ₂ NH ₂ |
| % Yield | 68 | 58 | 68 | 50 | Traces | Traces | Traces | Traces | NR* | NR* |

*NR: No Reaction

Table 1. Inhibition zone of compound 10a and 11 against *E. aerogenas* and *S. aureus*

| Compound No. | Concentration mg/ml | Inhibition zone (mm) | |
|--------------|---------------------|----------------------|------------------|
| | | <i>E. aerogenas</i> | <i>S. aureus</i> |
| 10a | 0.5 | 8 | 9 |
| | 0.3 | 7 | 8 |
| 11 | 0.5 | 19 | 10 |
| | 0.3 | 14 | 9 |

nitrogen atom of substituted aniline, where electron-releasing groups enhance nucleophilicity, while electron-withdrawing reduce the nucleophilicity.

The new compounds (**9a-d**) were characterized by elemental analyses, IR, MS, HRMS, ¹H-NMR and ¹³C-NMR spectral data. These data detailed in the experimental part are consistent with the predicted structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with calculated values.

In conclusion, this is the first example of palladium-catalyzed amination of chlorothienopyridone (**8**) with anilines, which have reduced nitrogen nucleophilicity, in absence of sterically hindered phosphine ligands. This catalytic activity of palladium acetate may be explained in terms of the presence of keto-ester functionality in ethyl 2-chloro-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate(**8**), which act as a chelate ligand to stabilizes catalytic palladium intermediate. These data and results encourage further investigations to explore the coupling of more anilines having electron-releasing groups, as well as, sterically hindered anilines.

2.2. Biology

The antibacterial activities of compounds **9(a-d)** and **10a** were assayed against *E. coli*, *B. subtilis*, *M. luteus*, *S. aureus*, *E. aerogenas* and *P. aeruginosa*. The initial investigation by agar diffusion test show that ethyl 7-cyclopropyl-2-(arylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylate (**9a-d**) have no activity against all tested bacteria; while 7-cyclopropyl-2-(phenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**10a**) showed weak activity against Gram-negative, *E. aerogenas* and Gram-positive *S. aureus* bacterial (Table 1). 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid (**11**) showed promising activities against *E. aerogenas* and *S. aureus* (Table 1) (Felmingham et al., 1985). In terms of structure-activity relationship replacing chlorine atom at position 2 by arylamino group results in decreased activity for 3-nitro-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine-5-carboxylic acid.

3. Experimental

3.1. Chemistry

Palladium (II) acetate, caesium fluoride, cyclopropylamine, aniline, *p*-fluoroaniline, *p*-toluidine and 3-acetyl-2,5-dichlorothiophene was purchased from Aldrich. Sodium hydride, sodium hydroxide, aluminium chloride, magnesium sulfate, triethylamine, dimethylformamide and ethyl 3-(*N,N*-dimethylamino)acrylate was purchased from Acros. *p*-Anisidine was purchased from Fluka. Silica gel for column chromatography was purchased from Macherew-Nagel GmbH & Co. KG (Germany). Carbon disulfide (CS₂) was dried over anhydrous phosphorous pentoxide (P₂O₅) and distilled. Thionyl chloride (SOCl₂) was purified by fractional distillation. Benzene and tetrahydrofuran were dried over sodium metal and distilled under a nitrogen atmosphere. Melting points were determined on a scientific melting point apparatus in open-capillary tubes. ¹H-NMR and ¹³C-NMR spectra were recorded on 400 MHz spectrometer (Bruker Avance III 400 MHz) (Al-Yarmouk University/Jordan) with TMS as the internal standard for solutions in CDCl₃, chemical shifts are expressed in δ units. Electron impact mass spectra (EIMS) were obtained using MASPEC system msw/A017(Al-Yarmouk University/Jordan). High-resolution mass spectra (HRMS) were measured by electrospray ionization

(ESI) technique on Bruker APEX-IV instrument (University of Jordan/Jordan), the samples were dissolved in chloroform, diluted in spray solution (methanol/chloroform) and infused using a syringe pump with a flow rate of 2 $\mu\text{L}/\text{min}$. Elemental analysis (CHNS) were determined by EA.96-mth (Al-Bayt University/Jordan). IR spectra were recorded on a MATTSON 500 FTIR spectrophotometer (Mutah University/Jordan).

3.2. Determination of inhibition zones (agar diffusion test)

The test microorganisms were cultured in a nutrient broth for 16 h. Bacterial test plates were prepared in nutrient agar medium in a density of 10^6 bacterial cell/ml. Aliquots of 0.5 and 0.3 mg/ml of freshly prepared solutions of compounds **10a** and **11** dissolved in DMSO were placed in a blank disk of 6 mm in diameter. Plates were then incubated at 37° C for 24 h. The zone of inhibition was determined as the diameter of the zone of inhibition around the disk.

3.2.1. Ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8**)

This compound was prepared from 3-acetyl-2,5-dichlorothiophene, ethyl 3-(*N,N*-dimethylamino) acrylate and cyclopropylamine by following literature procedures (El-Abadelah et al., 1997)

3.2.2. General procedure for the preparation of ethyl 7-cyclopropyl-2-(*N*-arylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylates (**9a-d**)

The particular aniline (~1.5 mmol), Pd(OAc)₂ (0.03 g, 0.14 mmol, 15%) and CsF (0.26 g, 1.96 mmol), were added to a stirred solution of ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno [2,3-b]pyridine-5-carboxylate (**8**) (0.20 g, 0.58 mmol) in DMF (5 ml). The reaction mixture was heated at 80–90°C for 48 h, the resulting solution was then cooled to room temperature, water (10 ml) was added, yellow to brown solid precipitate was obtained that dissolved in CHCl₃ and filtered to remove the insoluble material. The chloroform solution was then dried over MgSO₄ and evaporated under reduced pressure to give a brown to yellow residue, crude product was purified by column chromatography using silica gel and eluting with chloroform, ethyl acetate or acetonitrile.

3.2.2.1. Ethyl 7-cyclopropyl-2-(phenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b] pyridine-5-carboxylate (**9a**). This compound was prepared according to general procedure from ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate(**8**) (0.20 g, 0.58 mmol) and aniline (0.10 g, 1.07 mmol) to give a brown solid, reaction temperature 80–90°C; reaction time 24 h; ratio of the eluting mixture 1:2, v/v [CHCl₃:CH₃CN]. Yield 0.16 g (68%), m.p 237–240°C. Anal: calcd for C₁₉H₁₇N₃O₅ S (399.42): C, 57.13; H, 4.29; N, 10.52; S, 8.03. Found: C, 57.62; H, 4.43; N, 10.58; S, 8.02. IR: ν_{max} (KBr)/cm⁻¹ 3457, 1723, 1622, 1593, 1561, 1487, 1323, 1300, 1250, 1171, 1117, 1038, 812, 766. ¹H-NMR: (400 MHz, CDCl₃): δ 1.31(m, 2H) and 1.35(m, 2H)(H-2'/H-3'), 1.42(t, ³J = 7.2 Hz, 3H, CH₃CH₂O-), 3.56(m, 1H, H-1'), 4.43 (q, ³J = 7.2 Hz, 2H, OCH₂CH₃), 6.96(d, ³J = 7.2 Hz, 2H/H-2'', H-6''), 7.17(t, ³J = 7.6 Hz, 1H, H-4''), 7.33(dd, ³J = 7.2 Hz, ⁴J = 3.2 Hz 2H, H-3''/H-5''), 8.45(s, 1H, H-6), 11.56 (s, 1H, H-N). ¹³C-NMR: (100 MHz, CDCl₃): δ 7.9 (C-2', C-3'), 14.4(CH₃CH₂O), 36.6(C-1'), 61.7(-OCH₂CH₃), 116.7(C-5), 119.6(C-4''), 120.1(C-2'', C-6''), 120.3 (C-3a), 125.1(C-1''), 128.3(C-3'', C-5''), 138.7 (C-2), 140.9(C-3), 147.0(C-6), 153.1(C-7a), 163.9(CO₂Et), 173.6 (C-4). HRMS (ESI): found 400.09617 ([M+H]⁺) C₁₉H₁₈N₃O₅S requires 400.09672; found 422.07811 ([M+Na]⁺) C₁₉H₁₇N₃NaO₅S requires 422.0787; m/z (EI): 399.5 (M⁺, 13).

3.2.2.2. Ethyl 7-cyclopropyl-2-(4-methylphenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**9b**). This compound was prepared according to general procedure from ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate(**8**) (0.20 g, 0.58 mmol) and *p*-toluidine (0.09 g, 0.84 mmol) to give a brown solid, reaction temperature: 80–90°C; reaction time: 24 h; ratio of the eluting mixture: 1:3, v/v [CHCl₃:CH₃COOC₂H₅]. Yield = 0.14 g (58%), m.p 198–200°C. Anal: calcd for C₂₀H₁₉N₃O₅S (413.45): C, 58.10; H, 4.63; N, 10.16; S, 7.76. Found: C, 58.06; H, 4.90; N, 9.88; S, 7.48. IR: ν_{max} (KBr)/cm⁻¹ 3447, 1730, 1699, 1632, 1557, 1491, 1458, 1343, 1317, 1250, 1161, 1125, 814, 741. ¹H-NMR: (400 MHz, CDCl₃): δ 1.31(m, 2H) and 1.34(m, 2H)(H-2'/H-3'), 1.42(t, ³J = 8.0 Hz, 3H, CH₃CH₂O-), 3.55 (m, 1H, H-1'), 2.34 (s, 3H, C(4'')-CH₃), 4.43(q, ³J = 8.0 Hz, 2H, OCH₂CH₃), 6.85(d, ³J = 8.0 Hz, 2H,

H-2''/H-6''), 7.12(d, $^3J = 8.0$ Hz, 2H, H-3''/H-5''), 8.42(s, 1H, H-6), 11.54(s, 1H, H-N). $^{13}\text{C-NMR}$: (100MHz, CDCl_3): δ 7.9(C-2',C-3'), 14.4($\text{CH}_3\text{CH}_2\text{O}$), 21.1(C(4'')- CH_3), 36.6(C-1'), 61.7(- OCH_2CH_3), 116.6(C-5), 119.1(C-3a), 120.1(C-2'',C-6''), 120.3(C-1''), 128.8(C-3'',C-5''), 134.8(C-4''), 136.2(C-2), 141.1(C-3), 146.9(C-6), 153.2(C-7a), 163.9(- CO_2Et), 173.5(C-4). HRMS: (ESI): found 436.09376 ($[\text{M}+\text{Na}]^+$) $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_5\text{S}$ requires 436.0943; m/z (EI): 414 (M^+ ,68).

3.2.2.3. Ethyl 7-cyclopropyl-2-(4-methoxyphenylamino)-3-nitro-4-oxo-4,7-dihydrothieno- [2,3-b] pyridine-5-carboxylate (9c). This compound was prepared according to general procedure from ethyl 2-chloro -7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**8**) (0.20 g, 0.58 mmol) and *p*-anisidine (0.16 g, 1.30 mmol) to give a brown solid, reaction temperature: 80–90°C; reaction time: 24 h; ratio of the eluting mixture 1:1;v/v[CHCl_3 : CH_3CN]. Yield 0.17g (68%), m.p:192–195°C. Anal: calcd, for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_6\text{S}$ (429.4463): C,55.94; H,4.46; N,9.78; S,7.47. found:C,55.82; H,4.57; N,10.16; S,7.38. IR: ν_{max} (KBr)/ cm^{-1} 3447, 1732, 1699, 1632, 1562, 1491, 1346, 1314, 1248, 1121, 1032, 808. $^1\text{H-NMR}$: (400 MHz, CDCl_3); δ = 1.33(m,2H) and 1.37(m,2H), (H_2 -2'/ H_2 -3'), 1.42(t, $^3J = 7.2$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$ -), 3.56(m, 1H, H-1'), 3.82(s, 3H, C(4'')- OCH_3), 4.43(q, $^3J = 7.2$ Hz, 2H, OCH_2CH_3), 6.86(d, $^3J = 9.2$ Hz, 2H/H-2'', H-6''), 6.92(d, $^3J = 9.2$ Hz, 2H, H-3''/H-5''), 8.44(s, 1H, H-6), 11.57 (s, 1H, H-N). $^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ 7.9(C-2', C-3'), 14.4($\text{CH}_3\text{CH}_2\text{O}$), 36.6(C-1'), 55.4(C(4'')- OCH_3), 61.7(- OCH_2CH_3), 113.5(C-2'',C-6''), 116.7(C-5), 118.6(C-3a), 120.3(C-1''), 121.7(C-3'',C-5''), 132.0(C-2), 141.4(C-3), 146.9(C-6), 153.2(C-7a), 157.0(C-4''), 164.0(- CO_2Et), 173.5(C-4). HRMS (ESI): found 430.10673 ($[\text{M}+\text{H}]^+$), $\text{C}_{20}\text{H}_{20}\text{N}_3\text{O}_6\text{S}$ requires 430.1073; found 452.08868 ($[\text{M}+\text{Na}]^+$), $\text{C}_{20}\text{H}_{19}\text{N}_3\text{NaO}_6\text{S}$ requires 452.0892;m/z (EI):429 (M^+ ,35).

3.2.2.4. Ethyl 7-cyclopropyl-2-(4-fluorophenylamine)-3-nitro-4-oxo-4,7-dihydrothieno-[2,3-b]pyridine-5-carboxylate (9d). This compound was prepared according to general procedure from ethyl 2-chloro-7-cyclopropyl-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate(**8**) (0.20 g, 0.58 mmol) and *p*-fluoroaniline (0.10 g,0.90 mmol) to give a yellow solid (reaction temperature 80–90°C); reaction time 24 h; ratio of the eluting mixture 1:2,v/v[CHCl_3 : CH_3CN]. Yield 0.12 g (50%), m.p 220–225°C. Anal: calcd for $\text{C}_{19}\text{H}_{16}\text{FN}_3\text{O}_5\text{S}$ (417.41): C,54.67; H,3.86; N,10.07; S, 7.68. Found: C,53.79; H,3.79; N,9.75; S,7.38 . IR: ν_{max} (KBr)/ cm^{-1} 3457, 1723, 1622, 1593, 1561, 1487, 1323, 1300, 1249, 1171, 1117, 1038, 812, 766. $^1\text{H-NMR}$:(400 MHz, CDCl_3): δ 1.33(m,2H) and 1.36(m,2H) (H_2 -2'/ H_2 -3'), 1.42(t, $^3J = 7.2$ Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$ -), 3.57 (m, 1H, H-1'), 4.44(q, $^3J = 7.2$ Hz, 2H, OCH_2CH_3), 6.95(dd, $^3J = 6.8$ Hz, $^4J_{\text{H-F}} = 2.4$ Hz, 2H/H-2'',H-6''), 7.03(dd, $^3J = 6.8$ Hz, $^3J_{\text{H-F}} = 8.8$ Hz, 2H, H-3''/H-5''), 8.46 (s, 1H, H-6), 11.54 (s, 1H, H-N). $^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ 7.9(C-2',C-3'), 14.4 ($\text{CH}_3\text{CH}_2\text{O}$), 36.6(C-1'), 61.8(- OCH_2CH_3), 115.1(d, $^2J_{\text{C-F}} = 23$ Hz, C-3'',C-5''), 116.7(C-5), 120.2 (C-3a), 121.9(d, $^3J_{\text{C-F}} = 8$ Hz C-2'',C-6''), 128.0(C-1''), 135.0(C-2), 141.3(C-3), 147.0(C-6), 153.2(C-7a), 159.9(d, $^1J_{\text{C-F}} = 244$ Hz, C-4''), 163.9(- CO_2Et), 173.6(C-4). HRMS (ESI): found 418.08675 ($[\text{M}+\text{H}]^+$) $\text{C}_{19}\text{H}_{17}\text{FN}_3\text{O}_5\text{S}$ requires 418.0873; found 440.06869 ($[\text{M}+\text{Na}]^+$) $\text{C}_{19}\text{H}_{16}\text{FN}_3\text{NaO}_5\text{S}$ requires 440.0692;m/z (EI):417 (M^+ ,26).

3.2.2.5. Ethyl 7-cyclopropyl-2-(phenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b] pyridine-5-carboxylic acid (10a). This compound was prepared by hydrolysis of ethyl 7-cyclopropyl-2-(phenylamino)-3-nitro-4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carboxylate (**9a**) (0.04 g, 0.1 mmol) in 10% HCl (8ml) and few drops of ethanol, reaction temperature: 80–85°C under reflux condition; reaction time: 24 h. Yield 0.03 g (81%), m.p: 285–287°C. $^1\text{H-NMR}$:(400 MHz, CDCl_3): δ = 1.26(m, 2H) and 1.36 (m, 2H)(H_2 -2'/ H_2 -3'), 3.54(m, 1H, H-1'), 7.16(s, 3H, H- OCH_3), 7.34(d, $^3J = 7.6$ Hz, 2H, H-3''/H-5''), 7.09 (d, $^3J = 7.09$ Hz, 2H, H-2''/H-6''), 8.92(s, 1H, H-6), 10.72(s, 1H, H-N). $^{13}\text{C-NMR}$: (100 MHz, CDCl_3): δ 7.10 (C-2', C-3'), 37.60(C-1'), 118.9(C-2'',C-6''), 119.6(C-3a), 113.2(C-6), 118.3(C-5), 128.3(C-3'',C-5''), 148.4(C-3), 154.5(C-7a), 164.3(CO_2 -), 124.6(C-4'') and 175.4(C-4). m/z (EI):371 (M^+ ,49).

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Competing interests

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