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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW TETRAHYDROPYRIMIDINE DERIVATIVES

Yahia N. Mabkhot,[1] Nabila A. Kheder,[2,3,*] and Ahmad M. Farag[2]

[1]Department of Chemistry, Faculty of Science, King Saud University, 2455, Riyadh 11751, Saudi Arabia. [2]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt. [3]On leave to Department of Pharmaceutical Chemistry, Faculty of Pharmacy, King Khalid University, Abha, Saudi Arabia

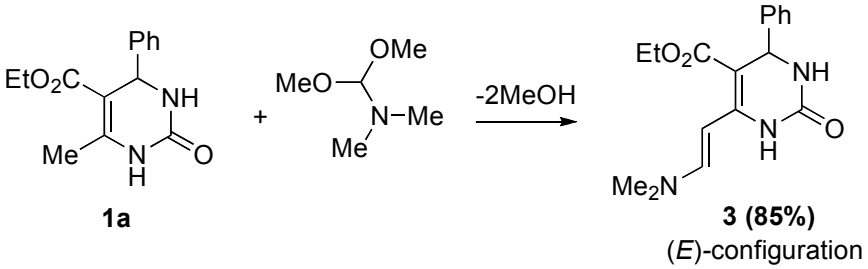
*Corresponding author: E-mail: nabila_abdelshafy@yahoo.com

Abstract – The utility of 1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a,b**), and 1,2-dihydropyrimidine-5-carboxylate (**2**) in the synthesis of some new functionalized pyrimidine derivatives such as 6-(2-(dimethylamino)vinyl)-1,2,3,4-tetrahydropyrimidine, 6-(1-cyano-2-(phenylamino)-2-thioxoethyl)-1,2,3,4-tetrahydropyrimidine and 4,6-distyryl-1,2-dihydropyrimidine derivatives is reported. Antimicrobial evaluation of some selected examples from the synthesized products was carried out and showed promising results.

Pyrimidine derivatives are reported to possess antibacterial,[1-3] antifungal[4,5] anticancer,[6,7] anti-inflammatory,[8,9] and cardioprotective effects.[10] In addition, certain pyrimidine derivatives are known to display antimalarial, antifilarial and antileshmainal activities.[11] Also, pyrimidine nucleus is considered as one of the most important classes of chemotherapeutic drugs. Many pyrimidine derivatives are used for thyroid drugs and leukemia.[12] In view of the these results and as an extension of our recent work concerned with the synthesis of heterocycles of interested biological activity[13-20] we decided to synthesize some new pyrimidine derivatives starting from the readily obtainable 1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives **1a**,[21] **1b**,[22] and dihydropyrimidine **2**[23] as highly versatile and useful building blocks for the synthesis of a wide variety of pyrimidine derivatives and to test their antimicrobial activity.

1,2,3,4-Tetrahydropyrimidine **1a** was found to react readily with dimethylformamide dimethyl acetal (*DMF-DMA*) to produce ethyl 6-(2-(dimethylamino)vinyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-

5-carboxylate (**3**) (Scheme 1). The IR spectrum of the product **3** showed absorption bands at, 1624, 1701, 3117, 3244 cm^{-1} due to two carbonyl groups, and two imino functions, respectively. Its ^1H NMR spectrum showed a triplet signal at δ 1.11 (J = 6.9 Hz) due to CH_3 protons, singlet signal at δ 2.85, characteristics for two methyl protons, a quartet signal at δ 3.96 (J = 6.9 Hz) due to CH_2 protons, a doublet signal at δ 5.17 (J = 3.6 Hz) due to CH proton, two doublets at δ 6.18 and δ 7.48 (J = 14.1 Hz) due to two olefinic protons, and two D_2O-exchangeable signals at δ 7.52 and 8.61 corresponding to two NH protons, in addition to an aromatic multiplet in the region δ 7.22-7.29. The value of the coupling constant for the ethylenic protons indicates that the pyrimidine **3** exists exclusively in the *E*-configuration.



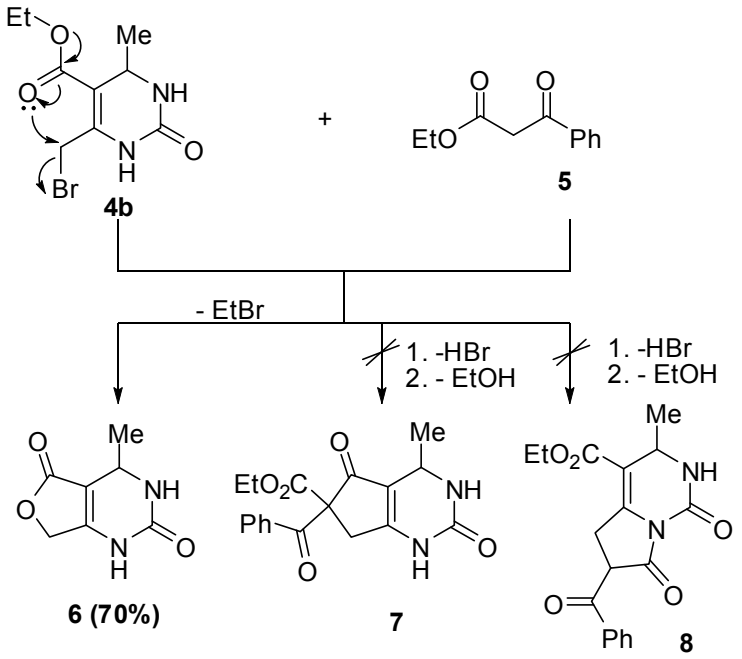
Scheme 1

The versatile synthons; ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**)[24] and ethyl 6-(bromomethyl)-2-oxo-4-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**),[24] were obtained from the bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**) and ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1b**), in acetic acid. Attempted reaction of compound **4b** with ethyl 3-oxo-3-phenylpropanoate (**5**), in order to obtain the expected structure **7** or **8**, was unsuccessful. Instead, compound **4b** underwent a thermal intramolecular cyclization reaction *via* elimination of bromoethane and afforded the corresponding 4-methyl-3,4-dihydrofuro[3,4-*d*]pyrimidine-2,5(1*H*,7*H*)-dione (**6**) (Scheme 2). Although ethyl 3-oxo-3-phenylpropanoate (**5**) is typically considered as a reagent, however, it behaves as an adequate high boiling solvent in this thermal cyclization reaction.

The first step of this reaction is connected with a nucleophilic attack of the lone pair of electrons of carbonyl oxygen in the ester group on the 6-bromomethyl group in **4b** followed by thermal elimination of bromoethane molecule under the reaction conditions to afford the final product **6**. The latter product was found to be identical in all respects [mp, mixed mp and IR spectrum] with that obtained from literature.[24]

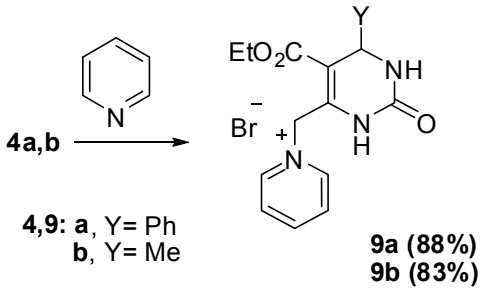
Pyridinium *N*-ylides are highly interesting compounds due to their reactivity as organic dipoles as well as their biological properties and applications. Usually, simple electron attracting groups, such as carbonyl, cyano etc., have been used to delocalize the negative charge. Less attention has been paid to the possibility of using heteroaryl groups as stabilizers except in the case of some tetrazole[25] and triazole stabilized ylides[26] which already described. Our work in this field has been concerned with the synthesis

of pyrimid-6-yl stabilized pyridine ylide[27] as a convenient root for producing highly stable dipole. Thus, pyridinium bromides **9a** and **9b** were prepared from **4a** or **4b** with an equivalent amount of pyridine in dry THF (Scheme 3).



Scheme 2

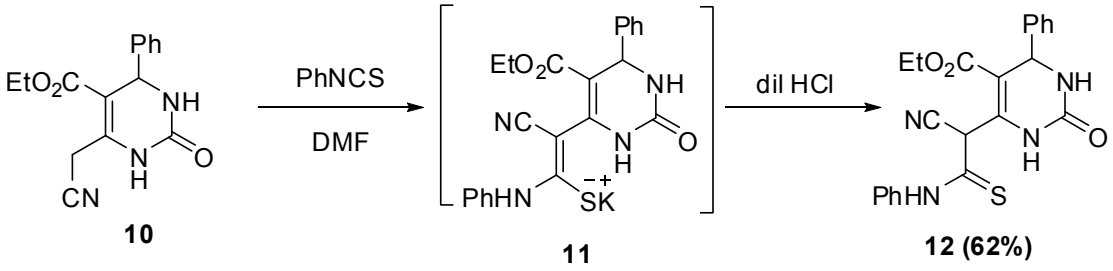
Reaction of the ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**) with potassium cyanide afforded the corresponding pyrimidine derivative **10**.[28]



Scheme 3

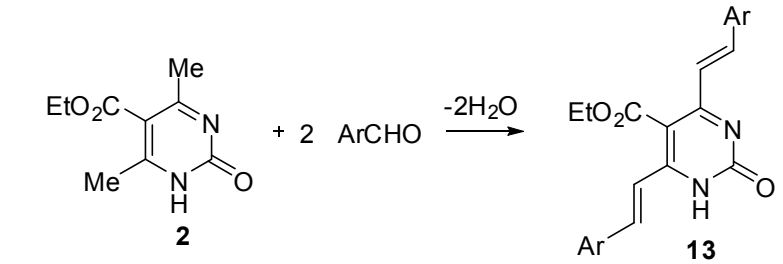
Treatment of the latter compound with phenyl isothiocyanate, in *N*,*N*-dimethylformamide, and in the presence of potassium hydroxide, at room temperature, followed by treatment with dilute hydrochloric acid, afforded the corresponding ethyl 6-(1-cyano-2-(phenylamino)-2-thioxoethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**12**) (Scheme 4).

Treatment of ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**2**) with the appropriate aromatic aldehydes in the presence of a catalytic amount of $ZnCl_2$, afforded the corresponding bis-arylidene derivatives **13a-c** (Scheme 5). The above reaction is assumed to proceed *via* loss of two water molecules.



Scheme 4

The Structure of the isolated products was assigned as ethyl 4,6-bis(substituted)-2-oxo-1,2-dihydropyrimidine-5-carboxylate **13a-c** based on their elemental analyses and their spectroscopic data. The ^{1}H NMR spectrum spectra of the isolated products showed in each case the absence of methyl signal and the value of the coupling constant for the ethylenic protons indicates that the pyrimidine **13** exists exclusively in the *E*-configuration.



13: Ar, a = Ph (70%)
b = 4-MeOPh (74%)
c = 4-ClPh (76%)

Scheme 5

In conclusion, the utility 1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a,b**), and 1,2-dihydropyrimidine-5-carboxylate (**2**) in the synthesis of some new functionalized pyrimidine derivatives of biological and pharmaceutical importance is reported.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The biological evaluation of the products **9b**, **12**, **13a** and **13c** were carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**),[21] ethyl 4,6-dimethyl-2-oxo-

1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1b**),[22] ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**2**),[23] ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**),[24] ethyl 6-(bromometh-yl)-2-oxo-4-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**)[24] and ethyl 6-(cyanomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**10**)[28] were prepared following the literature procedure.

Ethyl 6-(2-(dimethylamino)vinyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3).

A mixture of compound **1** (2.60 g, 10 mmol) and dimethylformamide dimethyl acetal (*DMF-DMA*) (1.33 mL, 10 mmol) in dry xylene (20 mL) was refluxed for 3 h, then left to cool. The precipitated product was filtered off, washed with EtOH and dried. Recrystallization from dioxane/ EtOH gave yellow crystals of compound **3** in 85% yield, mp 244-245 ^{o}C; IR (KBr) v 3244 (NH), 3117 (NH), 1701 (C=O), 1624 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.11 (t, 3H, CH_3, J = 6.9 Hz), 2.85 (s, 6H, 2NCH_3), 3.96 (q, 2H, CH_2, J = 6.9 Hz), 5.17 (d, 1H, J = 3.6 Hz), 6.18 (d, 1H, CH, J= 14.1 Hz), 7.22-7.29 (m, 5H), 7.48 (d,1H, CH, J= 14.1 Hz), 7.52 (s, 1H, D_2O-exchangeable NH), 8.61 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%) 315 (M^+, 20.0), 238 (100), 77 (36.0). Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.80; H, 6.67; N, 13.26%.

Attempted reaction of 6-bromomethylpyrimidine 4b with ethyl 3-oxo-3-phenylpropanoate (5).

To an ethanolic solution of 6-bromomethylpyrimidine **4b** (0.28 g, 1 mmol) and ethyl 3-oxo-3-phenyl-propanoate (**5**) (0.19 mL, 1 mmol) was added few drops of piperidine and the reaction mixture was refluxed for 4 h. The formed solid product was collected by filtration, washed with EtOH and purified by crystallisation from the DMF to afford a product identified as 4-methyl-3,4-dihydrofuro[3,4-*d*]pyrimidine- 2,5(1H,7H)-dione (**6**): Yield (70%), mp 268 °C. The latter product is assumed to be formed through an intramolecular cyclization of compound **4b** *via* thermal elimination of bromoethane and it was found to be identical in all respects (mp, mixed mp and IR spectrum) with an authentic sample prepared according to a literature procedure.[24] It is noteworthy that ethyl 3-oxo-3-phenylpropanoate (**5**) was not involved in above reaction but it acted as a suitable high boiling solvent for the above reaction. IR (KBr) v 3310 (NH), 3228 (NH), 1726 (C=O), 1662 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 3H, CH_3), 4.27 (d, 1H, CH, J = 5.1 Hz), 4.74 (s, 2H, CH_2), 7.3 (s, 1H, D_2O-exchangeable NH), 9.68 (s, 1H, D_2O-exchangeable NH). Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.12; H, 4.88; N, 16.64%.

Reaction of 6-bromomethylpyrimidine 4a or 4b with pyridine.

To a solution of 6-bromomethylpyrimidine **4a** or **4b** (10 mmol) in dry THF (20 mL), pyridine (0.8 mL, 10 mmol) was added. The reaction mixture was refluxed for 20 min, then left to cool to rt. The solid product was filtered off, washed with Et_2O and dried to afford the corresponding pyridinium salts **9a** and **9b**, respectively.

1-[(5-(Ethoxycarbonyl)-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]pyridiniumbromide (9a): Yield (88%), mp 197 ºC; IR (KBr) v 3230 (NH), 3093 (NH), 1700 (C=O), 1647 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.09 (t, 3H, CH_3, J = 6.9 Hz), 3.97 (q, 2H, CH_2, J = 6.9 Hz), 4.82 (s, 2H, CH_2), 5.14 (s, 1H), 7.22-7.35 (m, 10H, Ar-H), 7.70 (s, br., 1H, D_2O-exchangeable NH), 9.15 (s, br., 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{19}H_{20}BrO_3N_3$: C, 54.56; H, 4.82; N, 10.05. Found: C, 54.62; H, 4.89; N, 10.12%.

1-[(5-(Ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]pyridiniumbromide (9b): Yield (83%), mp 220 ºC; IR (KBr) v 3283 (NH), 3202 (NH), 1701 (C=O), 1659 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 3H, CH_3, J = 6.9 Hz), 1.22 (s, 3H, CH_3), 4.12 (q, 2H, CH_2, J = 6.9 Hz), 4.24 (s, 2H, CH_2), 5.58 (s, 1H) , 7.48 (s, br., 1H, D_2O-exchangeable NH), 8.17 (m, 2H), 8.64 (m, 1 H), 9.0 (d, 2H), 9.52 (s, br., 1H, D_2O-exchangeable NH). Anal. Calcd for $C_{14}H_{18}BrO_3N_3$: C, 47.20; H, 5.09; N, 11.80. Found: C, 47.29; H, 5.02; N, 11.88%.

Ethyl 6-(1-cyano-2-(phenylamino)-2-thioxoethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (12).

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in DMF (20 mL) was added the pyrimidine derivative **10**[28] (0. 57 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then the reaction mixture was poured over a cold solution of 0.5 N hydrochloric acid. The formed solid product was filtered off, washed with water, dried, and finally recrystallized from the EtOH to afford compound **12** in 62% yield, mp 175 ºC; IR (KBr) v 3209 (NH), 3101 (NH), 3051 (NH), 1697 (C=O), 1632 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.1 (t, 3H, CH_3, J = 6.9 Hz), 4.06 (q, 2H, CH_2, J = 6.9 Hz), 4.13 (s, 1H), 5.18 (d, 1H, CH, J = 2.4 Hz), 7.22-7.37 (m, 10H, Ar-H), 7.91 (s, br., 1H, D_2O-exchangeable NH), 8.0 (s, br., 1H, D_2O-exchangeable NH), 9.71 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 420 (M^+, 5.2), 419 (7.9), 374 (2.5), 373 (6.4), 339 (100.0), 291(13.7), 257 (60.7), 185 (52.8), 77 (85.2). Anal. Calcd for $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32%. Found: C, 62.80; H, 4.84; N, 13.28%.

Reaction of ethyl 4,6-dimethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (2) with aromatic aldehydes General procedure:

A mixture of the appropriate aromatic aldehyde (20 mmol), the pyrimidine derivative **2** (1.96 g, 10 mmol) and zinc chloride (1 mmol) was heated at 100 ºC with constant stirring for 1 h. After all starting material was consumed (TLC), the solution was cooled to ambient temperature. The precipitated crude product was purified by recrystallization from EtOH / DMF to afford the corresponding bis-arylidene derivative **13a-c**.

Ethyl 2-oxo-4,6-distyryl-1,2-dihydropyrimidine-5-carboxylate (13a): Yield (70%), mp 213 ºC; IR (KBr):

1623 (C=O), 1711 (C=O), 3024 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.28 (t, 3H, CH_3, J = 7.2 Hz), 4.57 (q, 2H, CH_2, J = 7.2 Hz), 6.95 (d, 2H, J = 15.85 Hz), 7.45-7.61 (m, 10H), 7.83 (d, 2H, J = 15.85 Hz), 12.10 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 373 (16.7), 372 (M^+, 44.2), 371 (54.3), 343 (100.0), 299 (73.2), 254 (12.3), 130 (16.0), 77 (24.2). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%. Found: C, 74.10; H, 5.35; N, 7.56%.

***Ethyl 4,6-bis(4-methoxystyryl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate* (*13b*):** Yield (74%), mp 220 ºC; IR (KBr): 1628 (C=O), 1712 (C=O), 3202 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (t, 3H, CH_3, J = 7.2 Hz), 3.81 (s, 6H, OCH_3), 4.45 (q, 2H, CH_2, J = 7.2 Hz), 7.0-7.05 (m, 6H), 7.60 (d, 4H, J = 8.7 Hz), 7.85 (d, 2H, J = 15.9 Hz), 11.9 (s, br., 1H, D_2O-exchangeable NH); MS *m/z* (%) 432 (M^+, 30.4), 403 (100.0), 359 (26.8), 315 (14.3), 285 (39.3), 121 (51.8), 77 (57.1). Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48%. Found: C, 69.49; H, 5.50; N, 6.56%.

Ethyl 4,6-bis(4-chlorostyryl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (13c): Yield (76%), mp > 300 ºC; IR (KBr): 1628 (C=O), 1709 (C=O), 3098 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29 (t, 3H, CH_3, J = 7.2 Hz), 4.41 (q, 2H, CH_2, J = 7.2 Hz), 7.27 (d, 2H, J = 15.9 Hz), 7.43-7.6 (m, 11H, Ar-H+NH); MS *m/z* (%) 368 (10.0), 367 (M^+ -EtOCO, 60.0), 174 (30.0), 127 (45.0), 86 (35.0). Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.60; H, 4.11; N, 6.35 %. Found: C, 62.67; H, 4.04; N, 6.30%.

ANTIMICROBIAL EVALUATION

Four of the newly synthesized target compounds were evaluated for their in vitro antibacterial activity against *Staphylococcus aureus* (RCMB 000106) and *Bacillis subtilis* (RCMB 000107) as examples of Gram-positive bacteria and *Pseudomonas aeruginosa* (RCMB 000102) and *Escherichia coli* (RCMB 000103) as examples of Gram-negative bacteria. They were also evaluated for their in vitro antifungal potential against *Aspergillus fumigatus* (RCMB 002003), *Geotrichum candidum* (RCMB 052006), *Candida albicans* (RCMB 005002) and *Syncephalastrum racemosum* (RCMB 005003) fungal strains. Agar-diffusion method was used for the determination of the antibacterial and antifungal activity.

Table 1

Microorganisms	Sample Tested				Standard (30 µg / ml)	
	9b	12	13a	13c		
FUNGI					Itraconazole	Clotrimazole
Aspergillus fumigatus (RCMB 002003)	15.3± 0.09	19.3± 0.09	16.5± 0.08	22.0± 0.10	28±0.05	26 ± 0.1
Geotrichum candidum (RCMB 052006)	13.4± 0.05	17.4± 0.10	14.8± 0.05	20.2± 0.50	27 ±0.1	23 ± 0.3

Candida albicans (RCMB 005002)	12.2± 0.08	15.2± 0.05	13.0± 0.05	16.5± 0.10	26 ±0.02	18 ± 0.1
Syncephalastrum racem-osum (RCMB 005003)	NA	NA	NA	NA	22 ±0.09	20 ± 0.2
Gram Positive Bacteria					Pencillin G	Streptomycin
Staphylococcus aureus (RCMB 000106)	17.9± 0.03	20.9± 0.03	18.9± 0.03	23.2± 0.02	29.48 ± 0.82	25 ± 0.2
Bacillis subtilis (RCMB 000107)	14.2± 0.1	22.2± 0.04	20.2± 0.04	24.3± 0.03	32.56 ± 0.56	29 ± 0.4
Gram negative Bacteria					Pencillin G	Streptomycin
Pseudomonas aeruginosa (RCMB 000102)	NA	NA	NA	NA	28.32 ± 0.10	24 ± 0.1
Escherichia coli (RCMB 000103)	11.4± 0.04	17.8± 0.1	12.4± 0.09	19.4± 0.50	33.56 ± 0.78	25 ± 0.3

NA: No activity, data are expressed in the form of mean ± SD.

Mean zone of inhibition in mm ± Standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (10 mg/mL) concentration of tested samples.

The results depicted in Table 1 revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive bacteria and Gram-negative bacteria strains and also against fungal strains. In general, most of the tested compounds revealed better activity against the Gram-positive bacteria rather than the Gram-negative bacteria and all compounds exhibited almost and no activity against *Syncephalastrum racemosum* and *Pseudomonas aeruginosa*.

Compounds **12** and **13c** showed promising results. Substitution at C-4 with phenyl or styryl substituent with electron withdrawing group in *para* position increased the activity. Also, substitution at C-6 with 1-cyano-2-(phenylamino)-2-thioxoethyl or styryl group increased the activity.

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