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Regioselective synthesis of N-formohydrazide and formyl pyrazole analogs as potent antimicrobial agents

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ABSTRACT

*A series of new (E)-N-(aryl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazides **2(a-g)** and 1-(aryl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3(a-g)** were prepared by the controlled Vilsmeier-Haack reaction. The reaction of (E)-1-aryl-2-[(1-thiophen-2-yl)ethylidene]hydrazines **1(a-g)** with Vilsmeier-Haack reagent under different reaction conditions afforded the compounds **2(a-g)** and **3(a-g)** in good yield. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral, x-ray diffraction studies and elemental analysis. The compounds were screened for their antimicrobial susceptibility against different bacterium and fungi species.*

Key words: Antibacterial, antifungal, formyl pyrazoles, hydrazines, inhibition.

INTRODUCTION

The transformation of a simple molecule to bioactive molecules of diverse biological applications is a worthwhile contribution in bioorganic chemistry. Formylation is an important process in organic synthesis. N-Formyl derivatives have been extensively used for the formylation of amines, amides, imines and alcohols [1]. Formyl derivatives are treated as useful synthons in organic and pharmaceutical chemistry; they have been extensively used as an intermediate in the synthesis of biologically potent molecules. They also exhibit remarkable biological activities, for instance, the formyl derivatives showed promising antimicrobial and antioxidant activities [2].

Pyrazoles represent a key motif in heterocyclic chemistry and occupy a prime place in medicinal chemistry due to their competence to exhibit a wide range of pharmacological activities such as antimicrobial [3, 4], anticancer [5], anti-inflammatory [6], anticonvulsant [7], antioxidant [8], antipyretic activities [9]. Pyrazoles having a functional group like aldehyde or carboxylate C-4 position have shown promising antimicrobial properties [10].

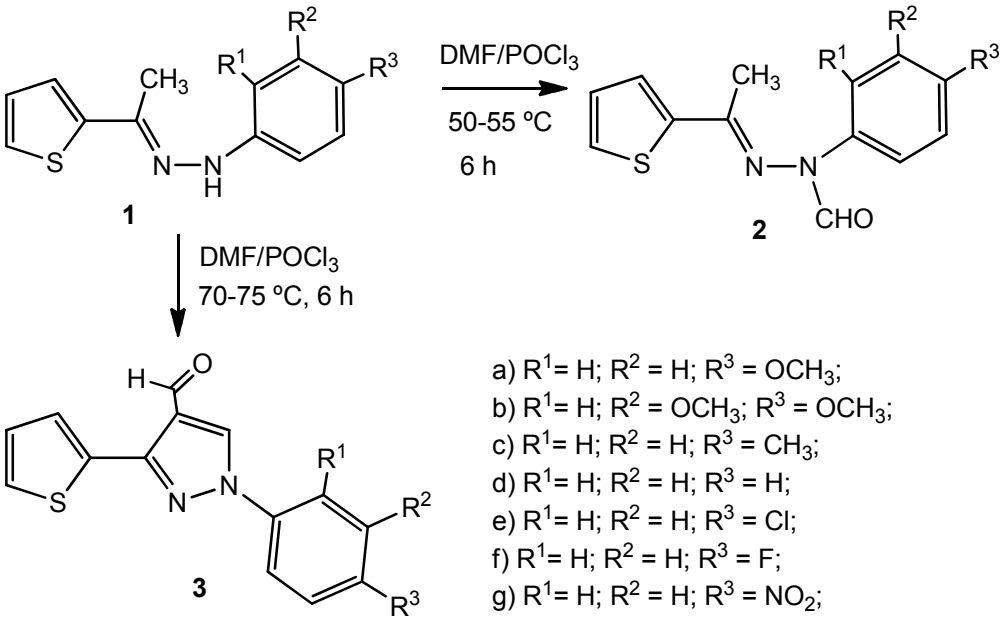
In view of the diverse synthetic and biological applications associated with the formyl derivatives, the task has been undertaken to synthesize new formyl derivatives and study their biological potency.

EXPERIMENTAL SECTION

We herein report the synthesis of series of novel **(**E)-N-(aryl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazides **2(a-g)** and 1-(aryl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3(a-g)** by Vilsmeier-Haack reaction. Initially, the required precursors (*E*)-1-aryl-2-[(1-thiophen-2-yl)ethylidene]hydrazines **1(a-g)** were prepared by the reaction of 2-acetyl thiophene and substituted phenylhydrazine hydrochlorides in the presence of sodium acetate in alcohol under reflux conditions.

In a typical reaction, to a solution of *E*)-1-aryl-2-[(1-thiophen-2-yl)ethylidene]hydrazine **1a** (0.2 mmol) in DMF, Vilsmeier-Haack reagent was added drop-wise. The reaction mixture was stirred at 50–55 °C for 6 hrs. After

completion of the reaction, the mixture was neutralized with sodium bicarbonate in ice cold water. The resulting solid was recrystallized from ethanol to get (E)-N-(aryl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide **2a** in 84% yield. However, with little excess of DMF and $POCl_3$, and at 65–70 °C for 6 hrs the reaction yielded 1-(4-methoxyphenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde **3a** in 92% yield. The reaction pathway is depicted in scheme-1.



Scheme-1: Synthetic route for formohydrazides and formyl pyrazoles

Antimicrobial activity of the synthesized compounds was done by paper disc diffusion method [11, 12]. The stock solution of the synthesized compounds were prepared by dissolving in minimum quantity of methanol and then diluted with water. The test compounds **2(a-g)** and **3(a-g)** at the concentration of 50 µg/mL concentrations in the nutrient agar media were screened for their antibacterial activity. The bacteria species *Escherichia coli, Salmonella typhimurium, Bacillus substilis* and the fungi species *Aspergillus niger, Aspergillus flavus* and *Fusarium oxysporium* were used as strains The antibiotics streptomycin and nystatin were used as standard drugs against bacteria and fungi organisms respectively.

EXPERIMENTAL SECTION

Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on a Nujol mull on Shimadzu 8300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and 100 MHz spectrophotometer respectively in $CDCl_3$ with TMS as an internal standard. The Chemical shifts are expressed in δ ppm. Mass spectra were obtained on Mass Lynx SCN781 spectrophotomer TOF mode. Elemental analysis was performed on a Thermo Finnigan Flash EA 1112 CHN analyzer. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane: ethyl acetate (6:2) as eluent.

General procedure for the synthesis of (E)-N-(Aryl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazides, 2(a-g): To a solution of (*E*)-1-aryl-2-[(1-thiophen-2-yl)ethylidene]hydrazine **1(a-g)** (0.2 mmol) in DMF, Vilsmeier-Haack reagent prepared by drop-wise addition of $POCl_3$ (1.5 ml) in ice cooled DMF (5 ml) was added slowly with swirling. The mixture was stirred at 50–55 °C for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water and then neutralized with sodium bicarbonate. The solid separated was filtered, washed thoroughly with ice cold water. The resulting solid was recrystallized from ethanol afforded the products **1(a-g)** in 76-88%.

General procedure for the synthesis of 1-(4-Methoxyphenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, 3(a-g): To a solution of (*E*)-1-aryl-2-[(1-thiophen-2-yl)ethylidene]hydrazine **1(a-g)** (0.2 mmol) in DMF, Vilsmeier-Haack reagent prepared by drop-wise addition of $POCl_3$ (3.0 ml) in ice cooled DMF (10 ml) was added slowly with swirling. The mixture was stirred at 65–70 °C for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water and then neutralized with sodium bicarbonate. The solid separated was filtered, washed thoroughly with ice cold water. The resulting solid was recrystallized from ethanol afforded the products **3(a-g)** in 80-94%.

RESULTS AND DISCUSSION

(E)-N-(4-Methoxyphenyl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2a:** Obtained from (E)-1-(4-methoxyphenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1b**), as white solid in 80% yield, mp 121-123 ºC. IR (Nujol, γ cm^{-1}): 1735 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.02 (dd, 2H), 7.18-7.42 (m, 3H, 5m ring), 7.55 (d, 2H, Ar-H), 9.36 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 14.66 (1C, CH_3), 55.60 (1C, OCH_3), 115.20 (2C), 124.60 (1C), 125.44 (1C), 125.80 (1C), 127.02 (1C), 127.36 (2C), 130.18 (1C), 155.10 (1C, C=N), 157.20 (1C), 166.54 (1C, C=O). MS (m/z): 274 (M+, 22), 246 (45), 125 (52), 121 (100). Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21%; Found: C, 61.21; H, 5.22; N, 10.26%.

(E)-N-(3,4-Dimethoxyphenyl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2b:** Obtained from (E)-1-(3,4-dimethoxyphenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1b**), as white crystalline solid in 78% yield, mp 100-103 ºC. IR (Nujol, γ cm^{-1}): 1728 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.421 (s, 3H, CH_3), 3.853 (s, 6H, OCH_3), 7.026-7.674 (m, 6H, Ar-H, 5m ring), 9.403 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 14.84 (1C, CH_3), 55.85 (2C, OCH_3), 105.11 (1C), 113.40 (1C), 120.32 (1C), 124.20 (1C), 125.08 (1C), 126.96 (1C), 127.44 (1C), 132.20 (1C), 155.36 (1C, C=N), 144.10 (1C), 149.33 (1C), 165.03 (1C, C=O). MS (m/z): 304 (M+, 18), 176 (38), 125 (36), 121 (100). Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20%; Found: C, 59.11; H, 5.18; N, 9.28%.

(E)-N'-(1-(Thiophen-2-yl)ethylidene)-N-(p-tolyl)formohydrazide, **2c:** Obtained from (E)-1-(1-(thiophen-2-yl)ethylidene)-2-(p-tolyl)hydrazine (**1c**) as white crystalline solid in 79% yield, mp 97-98 ºC. IR (Nujol, γ cm^{-1}): 1730 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.302 (s, 3H, CH_3), 7.326-7.500 (m, 3H, 5m ring), 7.623 (dd, 2H), 7.755 (dd, 2H), 9.442 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 14.90 (1C, CH_3), 22.10 (1C, CH_3), 124.86 (1C), 125.34 (1C), 125.82 (2C), 127.18 (1C), 127.48 (1C), 129.90 (2C), 133.60 (1C), 135.28 (1C), 154.88 (1C, C=N), 163.93 (1C, C=O). MS (m/z): 258 (M+, 22), 230 (41), 125 (23), 121 (100). Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84%; Found: C, 65.00; H, 5.41; N, 10.96%.

(E)-N-phenyl-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2d:** Obtained from 1-phenyl-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1d**) [13].

(E)-N-(4-chlorophenyl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2e:** Obtained from (E)-1-(4-chlorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1e**), as white crystalline solid in 78% yield, mp 105-107 ºC. IR (Nujol, γ cm^{-1}): 1733 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.181 (s, 3H, CH_3), 7.361-7.629 (m, 3H), 7.707 (dd, 2H), 7.832 (dd, 2H), 9.306 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 15.06 (1C, CH_3), 124.40 (1C), 125.14 (1C), 126.12 (2C), 127.26 (1C), 127.92 (1C), 129.42 (2C), 133.14 (1C), 134.20 (1C), 155.28 (1C, C=N), 164.90 (1C, C=O). MS (m/z): 280 (M+, ^{37}Cl, 09), 278 (M+, ^{35}Cl, 31), 250 (41), 125 (50), 125 (100). Anal. Calcd. for $C_{13}H_{11}ClN_2OS$: C, 56.01; H, 3.98; N, 10.05%; Found: C, 56.12; H, 3.92; N, 10.10%.

(E)-N-(4-fluorophenyl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2f:** Obtained from (E)-1-(4-fluorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1f**), as white crystalline solid in 80% yield, mp 131-132 ºC. IR (Nujol, γ cm^{-1}): 1720 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.380 (s, 3H, CH_3), 7.460-7.722 (m, 3H, 5m ring), 7.804 (dd, 2H), 8.089 (dd, 2H), 9.348 (s, 1H, -CHO). ^{13}C NMR ($CDCl_3$): δ 14.96 (1C, CH_3), 116.40 (2C), 123.26 (2C), 124.52 (1C), 125.66 (1C), 127.50 (1C), 127.86 (1C), 133.12 (1C), 155.18 (1C, C=N), 160.10 (1C), 165.30 (1C, C=O). Anal. Calcd. for $C_{13}H_{11}FN_2OS$: C, 59.53; H, 4.23; N, 10.68%; Found: C, 59.41; H, 4.20; N, 10.62%.

(E)-N-(4-nitrophenyl)-N'-(1-(thiophen-2-yl)ethylidene)formohydrazide, **2g:** Obtained from (E)-1-(4-nitrophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1g**), as white solid in 86% yield, mp 109-112 ºC. IR (Nujol, γ cm^{-1}): 1738 (s) (C=O str). ^{1}H NMR ($CDCl_3$): δ 2.368 (s, 3H, CH_3), 7.438-7.622 (m, 3H, 5m ring), 7.824 (dd, 2H), 8.12 (dd, 2H), 9.189 (s, 1H, -CHO). Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52%; Found: C, 53.88; H, 3.91; N, 14.42%.

The structure proofs of the synthesized new compounds were provided by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral studies, X-ray diffraction studies and elemental analysis. In IR spectra, the compounds **2(a-g)** showed a strong IR absorption bands in the region 1738-1720 cm^{-1} for aldehydic C=O stretching. The absorption bands expected due to N-H str of =N-N-H- group of the precursors hydrazones in the region 3280-3150 cm^{-1} were found absent. In ^{1}H NMR spectra, compounds showed a singlet in the region δ 9.248-9.426 ppm. further they showed the signals due to substituent and aromatic protons at the expected region.

In ^{13}C NMR, the compounds **2(a-g)** showed signals due to C=N function carbon atom in the region δ 154.00-156.00 ppm, and for carbonyl carbon in the region δ 163.00-166.00 ppm. Further all compounds showed the signals due to substituent carbons, aromatic carbons, and thiophene ring carbons in the expected region. All new compounds gave

significantly stable molecular ion peaks with a relative abundance ranging from 12-100%. The structure of the one of the synthesized compounds was confirmed by single crystal X-ray diffraction studies [13]. The satisfactorily elemental analysis further supports structure of the products.

1-(4-Methoxyphenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3a:** Obtained from (E)-1-(4-methoxyphenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1a**), as white solid in 86% yield, mp 143-144 ºC. IR (Nujol, γ cm^{-1}): 1726 (s) (C=O str), 1616 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 3.845 (s, 3H, OCH_3), 6.966 (d, 2H, Ar-H), 7.385-7.435 (m, 3H, 5m ring), 7.505 (d, 2H, Ar-H), 8.283 (s, 1H, C_5-H), 9.966 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 55.60 (1C, OCH_3), 112.46 (2C), 114.24 (1C, C-4), 114.88 (2C), 127.80 (1C), 128.32 (1C), 129.12 (1C), 131.30 (1C, C-5), 133.12 (1C), 136.64 (1C, C-3), 139.04 (1C), 157.30 (1C), 184.76 (1C, C=O). MS: m/z 285 (MH^+, 14), 284 (M^+, 36), 256 (44), 135 (51), 121 (100), 109 (33). Anal. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85%; Found C, 63.27; H, 4.12; N, 9.88%.

1-(3,4-Dimethoxyphenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3b:** Obtained from (E)-1-(3,4-dimethoxyphenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1b**), as white solid in 92% yield, mp 133-136 ºC. IR (Nujol, γ cm^{-1}): 1734 (s) (C=O str), 1612 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 3.865 (s, 6H, OCH_3), 6.963-7.486 (m, 6H, Ar-H, 5m ring), 8.408 (s, 1H, C_5-H), 10.006 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 55.80 (2C, OCH_3), 100.14 (1C), 103.20 (1C), 113.88 (1C, C-4), 118.12 (1C), 127.40 (1C), 128.10 (1C), 128.84 (1C), 130.24 (1C, C-5), 134.44 (1C), 136.80 (1C, C-3), 139.10 (1C), 149.10 (1C), 150.20 (1C), 185.20 (1C, C=O). MS: m/z 315 (MH^+, 14), 314 (M^+, 30), 286 (41), 135 (50), 151 (100), 109 (33). Anal. Calcd. for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91%; Found 61.05; H, 4.57; N, 8.84%.

1-(4-Methylphenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3c:** Obtained from (E)-1-(1-(thiophen-2-yl)ethylidene)-2-(p-tolyl)hydrazine (**1c**), as white solid in 86% yield, mp 106-108 ºC. IR (Nujol, γ cm^{-1}): 1728 (s) (C=O str), 1618 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 2.326 (s, 3H, CH_3), 7.066-7.237 (m, 3H, 5m ring), 7.369 (d, 2H, Ar-H), 7.480 (d, 2H, Ar-H), 8.342 (s, 1H, C_5-H), 9.902 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 21.84 (1C, CH_3), 114.66 (1C, C-4), 118.34 (2C), 127.60 (1C), 128.00 (1C), 128.66 (2C), 128.90 (1C), 131.96 (1C, C-5), 135.50 (1C), 136.22 (1C, C-3), 136.90 (1C), 138.20 (1C), 185.88 (1C, C=O). MS: m/z 269 (MH^+, 11), 268 (M^+, 28), 240 (49), 135 (42), 109 (22), 105 (100). Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44%; Found C, 67.06; H, 4.59; N, 10.31%.

1-Phenyl-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3d:** Obtained from 1-phenyl-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1d**), as white solid in 81% yield, mp 99-102 ºC. IR (Nujol, γ cm^{-1}): 1724 (s) (C=O str), 1615 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 7.466-7.782 (m, 8H, Ar-H, 5m ring-H), 8.188 (s, 1H, C_5-H), 9.923 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 114.19 (1C, C-4), 118.40 (2C), 126.70 (1C), 127.66 (1C), 128.10 (1C), 128.80 (1C), 129.10 (1C), 129.34 (2C), 130.22 (1C, C-5), 137.20 (1C, C-3), 138.84 (1C), 139.26 (1C), 184.20 (1C, C=O). MS: m/z 255 (MH^+, 10), 254 (M^+, 41), 226 (40), 135 (39), 109 (20), 91 (100). Anal. Calcd. for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02%; Found C, 66.01; H, 3.86; N, 11.09%.

1-(4-Chlorophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3e:** Obtained from (E)-1-(4-chlorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1e**), as white solid in 91% yield, mp 136-138 ºC. IR (Nujol, γ cm^{-1}): 1736 (s) (C=O str), 1622 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 7.103-7.255 (m, 3H, 5m ring), 7.408 (d, 2H, Ar-H), 7.515 (d, 2H, Ar-H), 8.446 (s, 1H, C_5-H), 9.980 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 115.10 (1C, C-4), 118.20 (2C), 127.92 (1C), 128.12 (1C), 129.10 (2C), 129.30 (1C), 130.80 (1C), 131.62 (1C, C-5), 135.46 (1C, C-3), 138.00 (1C), 139.20 (1C), 183.94 (1C, C=O). MS: m/z 290 (M^+, ^{37}Cl, 11), 288 (M^+, ^{35}Cl, 34), 262 (M^+, ^{37}Cl, 14), 260 (M^+, ^{35}Cl, 45), 226 (40), 135 (45), 125 (100), 109 (20). Anal. Calcd. for $C_{14}H_9ClN_2OS$: C, 58.23; H, 3.14; N, 9.70%; Found C, 58.32; H, 3.28; N, 9.58%.

1-(4-Fluorophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3f:** Obtained from (E)-1-(4-fluorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1f**), as white solid in 89% yield, mp 88-90 ºC. IR (Nujol, γ cm^{-1}): 1738 (s) (C=O str), 1625 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 7.166-7.323 (m, 3H, 5m ring), 7.426 (d, 2H, Ar-H), 7.584 (d, 2H, Ar-H), 8.507 (s, 1H, C_5-H), 10.100 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 114.12 (1C, C-4), 116.10 (2C), 118.24 (2C), 127.23 (1C), 127.98 (1C), 128.30 (1C), 131.72 (1C, C-5), 135.60 (1C), 135.94 (1C, C-3), 138.61 (1C), 158.20 (1C), 184.10 (1C, C=O). Anal. Calcd. for $C_{14}H_9FN_2OS$: C, 61.75; H, 3.33; N, 10.29%; Found C, 61.62; H, 3.42; N, 10.20%.

1-(4-Nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde, **3g:** Obtained from (E)-1-(4-nitrophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**1g**), as white solid in 90% yield, mp 172-173 ºC. IR (Nujol, γ cm^{-1}): 1720 (s) (C=O str), 1610 (m) (C=N str). ^{1}H NMR ($CDCl_3$): δ 7.186-7.368 (m, 3H, 5m ring), 8.129 (d, 2H, Ar-H), 8.283 (d, 2H, Ar-H), 8.364 (s, 1H, C_5-H), 10.031 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 114.84 (1C, C-4), 117.76 (2C), 122.30

(2C), 127.46 (1C), 128.00 (1C), 128.20 (1C), 131.14 (1C, C-5), 135.56 (1C, C-3), 138.40 (1C), 144.10 (1C), 146.22 (1C), 184.34 (1C, C=O). Anal. Calcd. for $C_{14}H_9N_3O_3S$: C, 56.18; H, 3.03; N, 14.04%; Found C, 56.11; H, 3.16; N, 14.13%.

In IR spectra, the compounds **3(a-g)** showed a strong IR absorption bands in the region 1738-1720 cm^{-1} for aldehyde C=O stretching and a medium absorption bands in the region 1625-1610 cm^{-1} for C=N (str) of the newly formed five membered ring. The absorption bands expected due to N-H (str) of =N-N-H- group of the precursors hydrazones in the region 3280-3150 cm^{-1} were found absent. These results support the formation of products. In ^1H NMR spectra, the compounds **3(a-g)** showed a consistent pattern signals as singlet in the region δ 8.304 -8.540 ppm. and δ 9.931-10.230 ppm. due to CHO proton and C_5-H respectively. Further all compounds showed the signals due to substituent and aromatic protons at the expected region.

In ^{13}C NMR, the consistent pattern signals were observed in the region δ 163.00-166.00 ppm. showed signals due to carbonyl carbon in the region δ 114.00-115.00 ppm. δ 131.00-132.00 ppm. and δ 135.00-136.00 ppm. for C-4, C-5 and C-3 atoms respectively. Further all compounds showed the signals due to substituent carbons, aromatic carbons, and thiophene ring carbons in the expected region. All new compounds gave significantly stable molecular ion peaks with a relative abundance ranging from 18-100%. The satisfactorily elemental analysis further supports structure of the products.

Antimicrobial activity: The experimental results of antibacterial activity of the synthesized compounds **2(a-g)** and **3(a-g)** tested against different bacterium were summarized in fig-1.

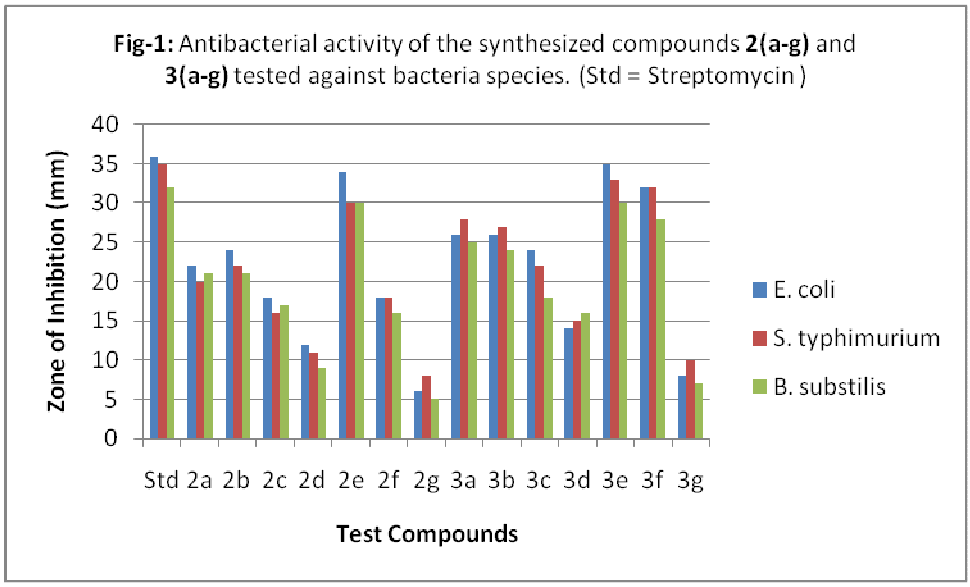


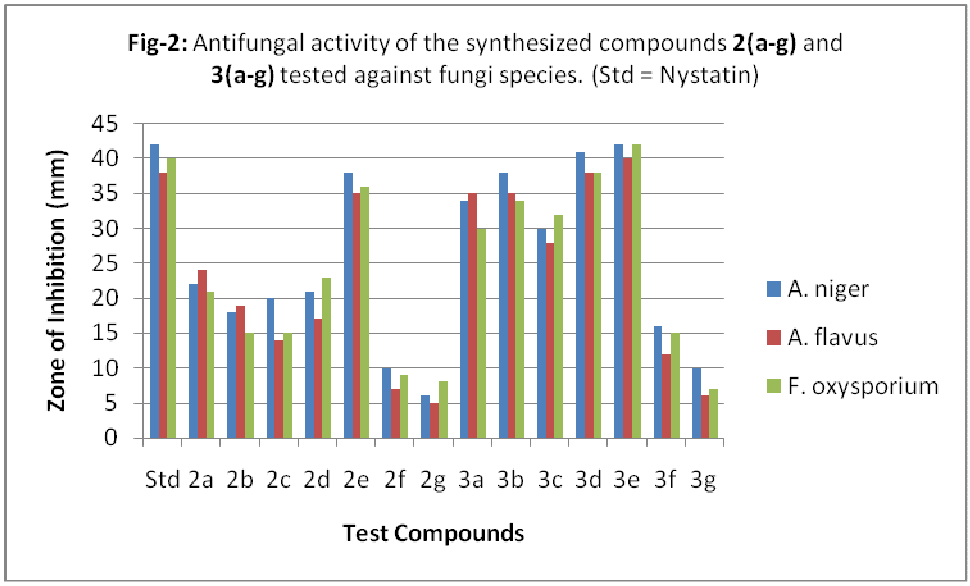
Fig-1: Antibacterial activity of the synthesized compounds **2(a-g)** and **3(a-g)** tested against bacteria species. (Std = Streptomycin)

The antibacterial activity of the synthesized compounds **2(a-g)** and **3(a-g)** tested against different bacteria showed varied antibacterial activity against the tested organisms.

From the experimental results, it is observed that the compounds **2(a-g)** exhibited relatively poorer activity compared to their formylpyrazole analogues **3(a-g)**. The compounds **2e** and **3e** showed excellent antibacterial activity in comparison with the standard streptomycin, this was attributed to the presence of chloro substitution. On the other hand, the compounds **2g** and **3g** having the strong electron withdrawing nitro substitution in the aromatic ring found to be less active against all the organisms tested.

The compound **3f** having fluoro substitution in the aromatic ring exhibited greater activity, and the compounds **3a, 3b** and **3c** exhibited remarkable activity, while the compound **3d** found moderately active against all the tested organisms. However; compared activity of these compounds with the corresponding formohydrazides **2a**, **2b**, **2c**, **2d** and **2f** showed relatively lesser activity of latter.

The experimental results of antifungal activity of the synthesized compounds **2(a-g)** and **3(a-g)** tested against different fungi strains were summarized in fig-2.



The results of antifungal activity of the synthesized compounds **2(a-g)** and **3(a-g)** tested against different fungal species revealed that, all the synthesized compounds showed moderate to good activity against the tested organisms. But the compounds **2f**, **2g** and **3f**, **3g** having nitro substitution exhibited least activity. The compound **2e** and **3e** showed remarkable antifungal activity in comparison with the standard nystatin against the tested organisms, this might be due to the presence of chloro substitution in the benzene ring. While the compound **3d** having no substitution in the benzene ring exhibited greater activity against all the fungi species tested. The compounds **2a**, **2b**, **2c** and **2d** showed moderate activity against the tested species. While the compounds **3a**, **3b** and **3c** showed promising activity.

CONCLUSION

The easy procedure for the synthesis of the series of formohydrazides and formylpyrazoles by a controlled Vilsmeier-Haack reaction, the efficacy of synthesized molecules as antimicrobial agents validates the significance of this study. Among the series of the compounds reported, 1-Phenyl-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde and 1-(4-Chlorophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbaldehyde acts as potential antifungal and antibacterial agents.

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