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Original Article

AN EFFICIENT AND SIMPLE SYNTHESIS OF 2, 3-DIHYDRO-1, 3, 4-THIADIAZOLES, PYRAZOLES AND COUMARINS CONTAINING BENZOFURAN MOIETY USING BOTH CONVENTIONAL AND GRINDING METHODS

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ABSTRACT

Objective: Green chemistry is the approach for synthesizing and using of chemicals that minimize risks to human and to the environments. The aim of this study describes the synthesis of some new thiadiazole, pyrazole and coumarin derivatives bearing benzofuran moiety by conventional, solvent free conditions (grindstone) and evaluating their antimicrobial effect.

Methods: Interaction of benzofuran derivative with different reagents under both grinding and conventional conditions.

Results: A facile, rapid and eco-friendly route with good yield for the synthesis of new thiadiazole, coumarin and pyrazole derivatives by grinding the reactants was reported. The structure of newly synthesized compounds was elucidated from spectral data (IR, NMR and mass). The investigation of antifungal and antibacterial screening data revealed that some of the tested compounds show moderate to low activities.

Conclusion: 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde was utilized as key intermediate for the synthesis of some new heterocycles, namely 2,3-dihydro-1,3,4-thiadiazole, pyrazole and coumarin derivatives under both grinding and convenential conditions. Most of the newly synthesized products revealed moderate activity against the tested microorganisms.

Keywords: 3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde, 2-Cyano acetohydrazide, Hydrazonoyl halides, Solvent-free, Green chemistry, Antimicrobial activity.

INTRODUCTION

The solvent-free reactions need shorter reaction times, simpler reactors, resulting simpler and more efficient work up procedure and easier separations than conventional method [1, 2]. On the other hand, 1,3,4-thiadiazoles have been screened for their antibacterial and antifungal [3,4], anti-inflammatory [5], anticancer [6], anti-amoebic [7] and anticonvulsant activities [8]. Furthermore, recent studies showed that benzofuran ring system fused with heterocyclic moieties exhibit a broad range of biological and pharmacological activities, including antimicrobial [9,10], anticancer [11,12], antioxidant [13], anti-inflammatory [14], anti tubercular [15] and antiprotozoal [16]. As an extension of our study [17, 18] and as a part of our program aiming at the synthesis of different heterocyclic derivatives, we report herein a simple and highly efficient method for the synthesis of 2, 3-dihydro-1,3,4-thiadiazoles, pyazole and coumarin derivatives bearing benzofuran moiety by grindstone.

MATERIALS AND METHODS

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University and were found within ± 0.4% of the theoretical values. 3-(Benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) [19, 20], benzyl hydrazine carbodithioate (**2**) [21] and hydrazonoyl halides **4a-d** [22-27] were prepared as previously reported.

Benzyl-N'-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl methylene)-hydrazine carbodithioate (3)

Conventional method

A mixture of 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) (1.44g, 5 mmol) and benzyl hydrazine carbodithioate (**2**) (0.96g, 5 mmol), in 2-propanol (20 mL) was stirred for 2 h. at room temperature. The resulting solid was collected and recrystallized from *N, N*-dimethylformamide to give **3**.

Solvent free

A mixture of **1** (1.45g, 5 mmol) and benzyl hydrazinecarbodithioate **2** (0.95g, 5 mmol) was ground with a pestle in an open mortar at room temperature for 3-5 min. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The mixture was then allowed to transfer to a round-bottomed flask and dried under high vacuum which facilitates the removal of water. The solid was washed with ethanol and recrystallized from *N,N*-dimethylformamide to afford product identical in all aspects to that prepared by method A. White powder; MP: 242-243°C; IR (KBr): 3375 (NH), 3062 (CH-aroma.), 1627 (C=N), 1593 cm^{-1}(C=C); ^{1}H NMR (DMSO-*d*6):δ = 4.50 (s, 2H, SCH_2), 7.22-8.02 (m,15H, Ar-H), 8.73 (s, 1H, CH=N), 9.06 (s, 1H, CH-pyrazole) and 13.37 ppm (s,1H, NH). Anal. Calcd. for $C_{26}H_{20}N_4OS_2$ (468.59): C, 66.64; H, 4.30; N, 11.96; S, 13.69. Found**:** C, 66.60; H, 4.34; N, 11.92; S, 13.65.

2-(5-Substituted 3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-1-(3-(benzofuran-2-yl)1-phenyl-1H-pyrazol-4-yl)methylene) hydrazines (8a-d)

Conventional method

A mixture of benzyl hydrazine carbodithioate derivative **3** (1.34g, 5 mmol), appropriate hydrazonoyl halides **4a-d** (5 m mol), and triethylamine (0.75 mL, 5 m mol) in ethanol (20 mL) were stirred for 2 h. at room temperature. The resulting solid was collected and recrystallized from DMF/EtOH to give 2, 3-dihydro-1,3,4-thiadiazoles **8a-d**,respectively.

Solvent free

Benzyl hydrazine carbodithioate derivative **3** (1.34g 5 m mol) and the appropriate hydrazonoyl halides **4a-d** (5 m mol), were mixed and ground with a pestle in an open mortar at room temperature followed by two drops of triethylamine. The mixture became sticky and adhered to the wall of the mortar firmly after a few seconds, which prevented the reactants from mixing thoroughly and coming

into sufficient contact. The grinding was continued for 5-7 min. and the reaction was monitored by TLC. The solid was washed with ethanol and recrystallized from DMF/EtOH to give **8a-d**, respectively.

Ethyl 5-[(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl-methylene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4] thiadiazole-2-carboxylate (8a)

Yellow powder; MP: 180-181°C; IR (KBr): 3057 (CH-arom.), 1735 (C=O), 1610(C=N), 1580 cm^{-1}(C=C); ^1H NMR(DMSO-*d6*): δ = 1.42 (t, 3H, *J* = 7*Hz*, CH_3), 4.19 (q, 2H, *J* = 7*Hz*, CH_2), 6.99-8.07 (m, 15H, Ar-H), 8.53 (s, 1H, CH=N) and 8.98 ppm (s,1H,CH-pyrazole); ^{13}C NMR: **(**DMSO-*d6*): δ 14.5 (CH_3), 63.6 (CH_2), 110.9-150 (Ar-C) and 167 ppm (C=O); MS: m/z 535 (M^+ + 1, 10), 242 (100). Anal. Calcd. for $C_{29}H_{22}N_6O_3S$ (534.59): C, 65.15; H, 4.15; N, 15.72; S, 6.00. Found**:** C, 65.19; H, 4.11; N, 15.76; S, 6.04.

1-{5-[(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-ylmethylene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-ethanone (8b)

Yellow powder; MP: 185-187°C; IR (KBr): 3068 (CH-aroma.), 1680 (C=O), 1610 (C=N), 1582 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ 2.40 (s, 3H, CH_3), 6.99-8.05 (m, 15H, Ar-H), 8.50 (s, 1H, CH=N) and 8.96 ppm (s,1H,CH-pyrazole); MS: m/z 504 (M^+, 20), 242(100); Anal. Calcd. for $C_{28}H_{20}N_6O_2S$ (504.56): C, 66.65; H, 4.00; N, 16.66; S, 6.36. Found: C, 66.61; H, 4.04; N, 16.62; S, 6.31.

2-(Benzofuran-2-yl-carbonyl)-5-[(3-(benzofuran-2-yl)-1-phenyl-1H-prrazol-4-yl-methylene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazole (8c)

Red powder; MP: 108-110°C; IR (KBr): 3068 (CH-aroma.), 1678 (C=O), 1610 (C=N), 1590 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ = 7.01-7.35 (m, 21H, Ar-H), 8.53 ppm (s, 1H, CH=N). Anal Calcd. for $C_{35}H_{22}N_6O_3S$ (606.65): C, 69.29; H, 3.66; N, 13.85; S, 5.29. Found: C, 69.25; H, 3.62; N, 13.89; S, 5.33.

1-{5-[(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-ylmethylene)-hydrazono]-4-phenyl-4,5-dihydro-[1,3,4]thiadiazol-2-yl}-phenylmethanone (8d)

Red powder; MP: 247-248°C; IR (KBr): 3068 (CH-aroma.), 1680 (C=O), 1600 (C=N), 1582 cm^{-1}(C=C); ^1H NMR (DMSO-*d6*):δ 7.01-7.35 (m, 21H, Ar-H), 8.51 ppm (s, 1H, CH=N); MS: m/z 566 (M^+, 20), 242 (100). Anal. Calcd. for $C_{33}H_{22}N_6O_2S$ (566.63):C, 69.95; H, 3.91; N, 14.83; S, 5.66. Found: C, 69.91; H, 3.95; N, 14.79; S, 5.70.

N-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-cyanoacetohydrazide (9)

Conventional method

To a solution of 2-cyanoacetohydrazide (0.99g, 5 mmol) in glacial acetic acid (10 mL), compound **1** (1.44g, 5 mmol) was added. The reaction mixture was stirred for 2 h. at room temperature. The resulting solid was collected and recrystallized from *N,N*-dimethylformamide to give **9**.

Solvent free

A mixture of **1** (1.44g, 5 mmol) and 2-cyanoacetohydrazide (0.99g, 5 mmol) was ground with a pestle in an open mortar at room temperature for 3-5 min. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC.

The mixture was then allowed to transfer to a round-bottomed flask and dried under high vacuum which facilitates the removal of water. The residue that formed was washed with ethanol and recrystallized from *N,N*-dimethylformamide to afford product identical in all aspects to that prepared by method A.

White powder; MP: 228-230°; IR (KBr): 3128 (NH); 3062 (CH-aroma.), 2256 (CN), 1685 (C=O), 1615 (C=N), 1591 cm^{-1} (C=C); ^1H NMR (DMSO-d6): δ 3.98 (s, 2H, CH_2), 7.25-7.82 (m, 11H, Ar-H), 8.50 (s, 1H, CH=N), 10.44 ppm (s, 1H, NH, D_2O-exchangeable); MS: m/z 368 (M^+-1, 100). Anal. Calcd. for $C_{21}H_{15}N_5O_2$ (369.38): C, 68.28; H, 4.09; N, 18.96. Found: C, 68.24; H, 4.13; N, 18.92.

3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2,5-dihydro-5-oxo-1H-pyrazole-4-carbonitrile (10)

Conventional method A

The hydrazone **9** (1.84g, 5 mmol) was boiled in acetic acid (10 mL) for 1 h. The resulting solid which was obtained on hot was collected and recrystallized from *N,N*-dimethylformamide to give **10**.

Conventional method B

A mixture of **1** (1.44g, 5 mmol) and 2-cyanoacetohydrazide (0.99g, 5 mmol) in acetic acid (10 mL) were heated under reflux for 2 h. The resulting solid which obtained on hot was collected and recrystallized from *N,N*-dimethylformamide to give **10**.

Solvent free

Compound **9** (1.48 g, 5 m mol), potassium hydroxide (0.56g, 10 mmol) and the few drops of water were ground with a pestle in an open mortar at room temperature for 3-5 min. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The solid was washed with water and recrystallized from *N,N*-dimethylformamide to afford **10** in excellent yield.

Red powder; MP: >340°C; IR (KBr): 3220, 3195 (2NH); 3062 (CH-aroma.), 2248 (CN),1668 (C=O), 1605 (C=N), 1589 (C=C) cm^{-1}; ^1H NMR (DMSO-*d6*): δ 7.28-7.92 (m, 12H, Ar-H + NH), 11.52 ppm (s,1H, NH); MS: m/z 368 (M^++1,10), 77 (100). Anal. Calcd. for $C_{21}H_{13}N_5O_2$ (367.36):C, 68.66; H, 3.57; N, 19.06. Found: C, 68.62; H, 3.53; N, 19.02.

5-3(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-1H-pyrazole-4-carbonitrile (11)

A solution of **10** (1.84g, 5 mmol) in phosphorous oxychloride (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled then poured into ice-water with stirring. The solid that formed was collected by filtration and recrystallized from *N,N*-dimethylformamide to give **11**.

Brown powder; MP: >330°C; IR (KBr): 3190 (NH); 3062 (CH-aroma.), 2230 (CN), 1602 (C=N), 1590 cm^{-1} (C=C); MS: m/z 385, 386 (M^+) (15, 4%), 77 (100). Anal. Calcd. for $C_{21}H_{12}ClN_5O$ (385.81): C, 65.38; H, 3.14; Cl, 9.19; N, 18.15. Found: C, 65.34; H, 3.10; Cl, 9.15; N, 18.11.

General method for Synthesis of 12-14

Conventional method

A mixture of **11** (1.84g, 5 mmol) and the appropriate heterocyclic amines such as 2-aminotriazole, 4-phenyl-5-aminopyrazole and 2-aminobenzimidazole (5 mmol) in dry dioxane (15 mL) and triethylamine (0.5 mL) was reflux for 5h. The solvent was evaporated under vacuum and the resulting residue was triturated with water. The solid that formed was filtered off and recrystallized from *N,N*-dimethylformamide to give the corresponding compounds **12-14**, respectively.

Solvent free

A mixture of **11** (1.84g, 5 mmol), the appropriate amines (5 mmol) and three drops of triethylamine was ground with a pestle in an open mortar at room temperature for 3-5 min. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The mixture was transfer to a round-bottomed flask and dried under high vacuum which facilitates the removal of water. The solid was washed with ethanol and recrystallized from *N,N*-dimethylformamide to afford product identical in all aspects to that prepared by method A.

3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d][1,2,4] triazolo[4,3-a]pyrimidin-4-amine (12)

Peige powder; MP: >340°C; IR (KBr): 3315, 3220, 3195 (NH, NH_2), 3062 (CH-aroma.), 1615 (C=N), 1590 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ 7.28-7.92 (m, 14H, Ar-H + NH_2), 10.52 ppm (s, 1H, NH); Anal. Calcd. for $C_{23}H_{15}N_9O$ (433.42): C, 63.74; H, 3.49; N, 29.08. Found: C, 63.70; H, 3.45; N, 29.04.

3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-7-phenyl-1H-dipyrazolo[1,5-a: 3',4'-d]pyrimidin-4-amine (13)

Brown powder; MP: 260-262°C; IR (KBr): 3340, 3230, 3143 (NH, NH_2); 3062 (CH-aroma.), 1610 (C=N), 1587 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ 7.20-7.99 (m, 19H, Ar-H + NH_2), 11.35 ppm (s, 1H, NH); MS: m/z 508 (M^+, 15), 77 (100). Anal. Calcd. For $C_{30}H_{20}N_8O$ (508.53): C, 70.86; H, 3.96; N, 22.03. Found: C, 70.84; H, 3.92; N, 22.00.

3-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1H-pyrazolo [3,4-d]benzoimidazolo[1,2-a]pyrimidin-4-amine (14)

Peige powder; MP: 180-182°C; IR (KBr): 3320, 3223, 3150 (NH, NH_2); 3062 (CH-aroma.), 1607 (C=N), 1589 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ 7.20-7.99 ppm (m, 18H, Ar-H + NH + NH_2). Anal. Calcd. for $C_{28}H_{18}N_8O$ (482.5): C, 69.70; H, 3.76; N, 23.22. Found: C, 69.74; H, 3.72; N, 23.23.

Synthesis of 4-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1,5-dihydro pyrazolo[3,4-c]pyrazol-3-amine (15)

Conventional method

A mixture of **11** (1.84g, 5 mmol) and hydrazine hydrate (1 ml, 10 mmol) in absolute ethanol (15 ml) was refluxed for 3h. The precipitate that formed on hot was filtered off and recrystallized from *N,N*-dimethylformamide to give the desired product **15**.

Solvent free

A mixture of **11** (1.84g, 5 mmol) and hydrazine hydrate (1 mL, 10 mmol) was thoroughly ground with a pestle in an open mortar at room temperature for 3-5 min. until the mixture turned into a melt. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC.

The solid formed was washed with water and recrystallized from *N,N*-dimethylformamide to give **15**. Brown powder; MP: 310-312°C; IR (KBr): 3429, 3306, 3190 (NH, NH_2); 3058 (CH-aroma.), 1617 (C=N), 1581 cm^{-1} (C=C). Anal. Calcd. for $C_{21}H_{15}N_7O$ (381.39): C, 66.13; H, 3.96; N, 25.71. Found: C, 66.17; H, 3.92; N, 25.75.

Synthesis of 3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-5,7-dimethyl-1H-pyrazolo[3',4':3,4]pyrazolo[1,5-a]pyrimidine(16)

Conventional method

Equimolar amounts of **15** (1.90g, 5 mmol) and acetyl acetone (0.5 ml, 5 mmol) in acetic acid (20 mL) was heated under reflux for 1 h. The solid formed was collected and recrystallized from *N,N*-dimethylformamide to give the title compound.

Solvent free

A mixture of **15** (1.90g, 5 mmol) and acetylacetone (5 mmol) was thoroughly ground with a pestle in an open mortar at room temperature for 3-5 min. until the mixture turned into a melt. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The solid was washed with water and recrystallized from *N,N*-dimethylformamide to afford **16**. Brown crystals; MP: 180-182°C; IR (KBr): 3283 (NH), 3021 (CH-aroma.), 1604 (C=N), 1589 cm^{-1} (C=C); ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.05-7.98 ppm (m, 13H, Ar-H and NH proton); MS: m/z 445 (M^+,100). Anal. Calcd. for $C_{26}H_{19}N_7O$ (445.48): C, 70.10; H, 4.30; N, 22.01. Found: C, 70.14; H, 4.34; N, 22.06.

Synthesis of imino coumarin derivatives 17-19

Conventional method

To a solution of hydrazone **9** (1.84g, 5 mmol) and appropriate aldehydes namely, salicyaldehyde, 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde [28,29] or 7-hydroxy-5-methoxy-2-oxo-2*H*-chromene-6-carbaldehyde [29] (5 mmol) in ethanol (15 mL), few drops of piperidine were added and the reaction mixture was refluxed for 3 h. The precipitate that formed was filtered off washed with ethanol and recrystallized from *N, N*-dimethylformamide to give the corresponding **17-19**, respectively.

Solvent free A

To 5 mmole of hydrazone **9** and 5 mmoles of aldehydes, three drops of piperidine were added and grind using a pestle at room temperature for 3-5 until the mixture turned into a melt, during which time a color change occurred (the change is typically colorless to yellow or orange). The mixture was then transferred to a round-bottomed flask and dried under high vacuum (which facilitates the removal of water and residual piperidine) to afford 92% of the title compound, identical to that prepared via ethanol reflux.

Solvent free B

A mixture of **1** (1.44g, 5 mmol) and **23** (1g, 5 mmol) was ground with a pestle in an open mortar at room temperature for 3-5 min. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The mixture was then transfer to a round-bottomed flask and dried under high vacuum which facilitates the removal of water. The solid was washed with ethanol and recrystallized from *N,N*-dimethylformamide to afford product identical in all aspects to that prepared by method A.

N-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-imino-2H-chromene-3-carbohydrazide (17)

Yellow powder; MP: 160-162°C; IR (KBr): 3390 broad 2(NH), 3062 (CH-aroma.), 1660 (C=O), 1604 (C=N), 1589 cm^{-1} (C=C); ^1H NMR (DMSO-*d6*): δ 6.73-7.92 (m,17H, Ar-H + NH), 8.53 (s,1H,CH=N), 9.50 ppm (s, 1H, NH); ^{13}C NMR (DMSO-*d6*): δ 109.9-133.12 (Ar-C), 143.8, 160.6 (C=N), 163.8 ppm (C=O); MS: m/z 473 (M^+, 20), 368 (100). Anal. Calcd. for $C_{28}H_{19}N_5O_3$ (473.48): C, 71.03; H, 4.04; N, 14.79. Found: C, 71.07; H, 4.08; N, 14.86.

***N*-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-imino-5-methoxy-8-methyl-6-oxo-2,6-dihydropyrano[3,2-g]chromene-3-carbohydrazide (18)**

Yellow powder; MP: 305-307°C; IR (KBr): 3393 broad 2(NH), 3072 (CH-aroma.), 1657 (C=O), 1602 (C=N), 1589 cm^{-1} (C=C);^1H NMR (DMSO-*d6*): δ 2.23 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.04 (s, 1H, CH-10), 6.75 (s, 1H, CH-7), 6.73-7.92 (m,12H, Ar-H), 8.20 (s, 1H, CH=N), 9.90 (s, 1H, NH), 10.20 ppm (s, 1H, NH); MS: m/z 585 (M^+, 16), 273 (100). Anal. Calcd. for $C_{33}H_{23}N_5O_6$ (585.57): C, 67.69; H, 3.96; N, 11.96. Found: C, 67.65; H, 4.00; N, 11.93.

N-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-imino-5-methoxy-8-oxo-2,8-dihydropyrano[3,2-g]chromene-3-carbohydrazide (19)

Orange powder; MP: 286-288°C; IR (KBr): 3385 broad 2(NH), 3072 (CH-aroma.), 1650 (C=O), 1602 (C=N), 1589 cm^{-1} (C=C);^1H NMR (DMSO-*d6*): δ 4.01 (s, 3H, OCH_3), 6.33 (d, 1H, CH-7), 7.34 (d, 1H, CH-6), 6.73-7.92 (m, 15H, Ar-H + 2NH), 8.45 ppm (s, 1H, CH=N); MS: m/z 571 (M^+,16), 273 (100). Anal. Calcd. for $C_{32}H_{21}N_5O_6$ (571.54):C, 67.25; H, 3.70; N, 12.25. Found: C, 67.21; H, 3.74; N, 12.23.

Synthesis of coumarin derivatives 20-22

Conventional method: A mixture of each of compounds **17-19** (5 mmol) and hydrochloric acid 50%, (10 mL), was warmed with stirring for 30 min. The resulting solid was collected, washed with water and recrystallized from *N,N*-dimethylformamide to give compounds **20-22**.

Solvent free

To 5 mmol (1.84g) of hydrazone **9** and 5 mmol aldehydes, three drops of piperidine were added and grind using a pestle at room temperature for 7-10 min. until the mixture turned into a melt, during which time a color change occurred (the change is typically colorless to yellow or orange). The mixture was then allowed to stand at room temperature until it solidified, transferred to a round-bottomed flask and dried under high vacuum (which facilitates the removal of water and residual piperidine) to afford the desired product in excellent yield.

N-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-2-oxo-2H-chromene-3-carbohydrazide (20)

Brown powder; MP: 242-244°C; IR (KBr): 3335 (NH), 3072 (CH-aroma.), 1688 (C=O), 1603 (C=N), 1587 cm^{-1} (C=C);^1H NMR ($CDCl_3$):

δ 7.22-7.83 ppm (m,16H, Ar-H), 8.70 (s, 1H, CH=N), 13.50 (s, 1H, NH); ^{13}C NMR **(**DMSO-*d*6): δ 107.9-133 (Ar-C), 143.2 (C=N),158.6 ppm (C=O); MS: m/z 474 (M^+, 9), 368 (100). Anal. Calcd. for $C_{28}H_{18}N_4O_4$ (474.47): C, 70.88; H, 3.82; N, 11.80. Found: C, 70.84; H, 3.78; N, 11.85.

N-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-5-methoxy-8-methyl-2,6-dioxo-2,6-dihydropyrano[3,2-g]chromene-3-carbohydrazide (21)

Orange powder; MP: >340 °C; IR (KBr): 3429 (NH), 3062 (CH-arom.), 1651 (C=O), 1596 cm^{-1} (C=N);^{1}H NMR **(**DMSO-*d*6): δ 2.26 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.04 (s,1H, CH-10), 6.75 (s, 1H, CH-7), 6.73-7.92 (m, 12H, Ar-H), 8.20 (s, 1H, CH=N), 10.20 ppm (s, 1H, NH); MS: m/z 586 (M^+,14), 273 (100). Anal. Calcd. for $C_{33}H_{22}N_4O_7$ (586.55): C, 67.57; H, 3.78; N, 9.55. Found: C, 67.53; H, 3.74; N, 9.59.

N-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-5-methoxy-2,8-dioxo-2,8-dihydropyrano[3,2-g]chromene-3-carbohydrazide (22)

Brown powder; MP: >340°C; IR (KBr): 3330 (NH), 3072 (CH-aroma.) 1650 (C=O), 1605 (C=N), 1590 cm^{-1} (C=N);^{1}H NMR **(**$CDCl_3$): δ 4.26 (s, 3H, OCH_3), 6.33 (d, 1H, CH-7), 7.12 (d, 1H, CH-6), 7.25-8.16 (m, 14H, Ar-H + NH), 8.44 ppm (s, 1H, CH=N); MS: m/z 571 (M^+ - 1, 16), 273 (100). Anal. Calcd. for C $_{32}H_{20}N_4O_7$: (572.52):C, 67.13; H, 3.52; N, 9.79. Found: C, 67.17; H, 3.56; N, 9.75.

N-((3-(benzofuran-2-yl)-2,3-dihydro-1-phenyl-1H-pyrazol-4-yl)methylene)-2-cyano-3-phenylacrylohydrazide (24)

Conventional method

To a solution of **9** (1.84g, 5 mmol) and benzaldehyde (0.5 mL, 5 mmol) in ethanol (10 mL), two drops of piperidine were added and the reaction mixture was stirred for 1 h. The formed solid was filtered off and recrystallized from *N,N*-dimethylformamide to give **24**.

Solvent free

To 5 mmol (1.84g,) of compound **9** and 5 mmol of benzaldehyde, two drops of piperidine were added and grind at room temperature for the appropriate time to complete the reaction. After completion of the reaction, as indicated by TLC The reaction mixture was transferred to a round-bottomed flask and dried under high vacuum which facilitates the removal of water and residual piperidine. The solid was washed with ethanol and recrystallized from *N,N*-dimethylformamide to afford product identical in all aspects to that obtained by ethanol reflux.

Orange powder; MP: 200-201°C; IR (KBr): 3329(NH), 3062 (CH-arom.), 2210 (CN), 1678 (C=O), 1602 cm^{-1} (C=N). Anal. Calcd. for $C_{28}H_{19}N_5O_2$ (457.48): C, 73.51; H, 4.19; N, 15.31. Found: C, 73.55; H, 4.23; N, 15.34.

Synthesis of 2-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl)-4-benzylidene-4H-pyrazol-3-amine (25)

Conventional method

A mixture of **24** (2.28g, 5 mmol) and hydrazine hydrate (1 g, 1 mL, 10 mmol) in absolute ethanol (15 mL) was refluxed for 3 hrs. The precipitate that formed on hot was filtered off and recrystallized from acetic acid to give the title compound.

Solvent free

A mixture of **24** (2.28g, 5 mmol) and hydrazine hydrate (1 mL, 10 mmol) was ground with a pestle in an open mortar at room temperature for 3-5 min. until the mixture turned into a melt. The initial syrupy continued for 5-7 min. and the reaction was monitored by TLC. The solid was washed with water and recrystallized from acetic acid to give **25**.

Peige powder; MP: 270-272°; IR (KBr): 3429, 3239, 3136 (NH_2, NH), 3062 (CH-arom.), 1602 cm^{-1} (C=N).; ^{1}H NMR **(**$CDCl_3$): δ 6.99-7.88 (m, 19H, Ar-H + NH_2), 8.85 (s, 1H, CH=N), 9.33 ppm (s, 1H, NH); ^{13}C NMR **(**$CDCl_3$): δ 111.9-139.1 (Ar-C), 141.3, 160.8 ppm (2C=N). Anal. Calcd. for $C_{28}H_{21}N_7O$ (471.51): C, 71.32; H, 4.49; N, 20.79. Found: C, 71.36; H, 4.45; N, 20.75.

Biological activity

Antimicrobial activity of the newly synthesized compounds was determined *in vitro* by standardized disc – agar diffusion method [30].

Antibacterial activity

Newly prepared compounds were screened *in vitro* for their antibacterial activity against Gram- positive bacteria: *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635), Gram – negative bacteria: *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028).

Bacterial cultures were grown in nutrient broth medium at 30 °C. After 16 h of growth, each microorganism, at a concentration of 10^8cells/mL, was inoculated on the surface of Mueller-Hinton agar plates using sterile cotton swab. Subsequently, uniform size filter paper disks (6 mm in diameter) were impregnated by equal volume (10 µl) from the specific concentration of dissolved compounds and carefully placed on surface of each inoculated plate.

The tested compounds were dissolved in dimethylformamide (DMF) solvent and prepared in two concentrations; 100 and 50 mg/ml and then 10 µl of each preparation was dropped on disk of 6 mm in diameter and the concentrations became 1 and 0.5 mg/disk respectively. In the case of insoluble compounds, the compounds were suspended in DMF and vortexed then processed. The plates were incubated in the upright position at 36ºC for 24h and then the plates were examined for the formation of zone inhibition.

Three replicates were carried out for each dissolved compound against each of the test organism. Simultaneously, addition of the respective solvent instead of dissolved compound was carried out as negative controls. After incubation, the diameters of the growth inhibition zones formed around the disc were measured with transparent ruler in millimeter, averaged and the mean values were tabulated. The antibiotic chloramphenicol was used as standard reference in the case of Gram – negative bacteria; Cephalothin was used as standard reference in the case of Gram – positive bacteria. Zones of inhibition were determined for the tested compounds and the results were summarized in table 2.

Antifungal activity

Active inoculum for experiments were prepared by transferring many loopfuls of spores from the stock cultures to test tubes of sterile distilled water that were agitated and diluted with sterile distilled water to achieve optical densitycorresponding to $2.0x10^5$spore/ml. inoculum of 0.1 % suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes then the same procedure was followed as described above, the inhibition zones of the tested compounds were measured after 3-4 days incubation at 28°C.

Cycloheximide was used as standard reference in the case of yeasts and fungi. Zones of inhibition were determined for the tested compounds and the results were summarized in table 3.

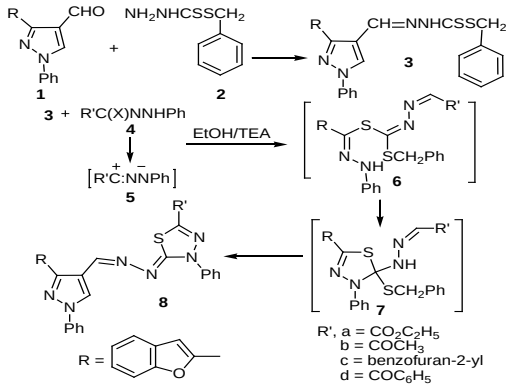
RESULTS AND DISCUSSION

Reaction of 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**), with benzyl hydrazinecarbodithioate (**2**) in 2-propanol at room temperature afforded benzyl-N'-(3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-yl-methylene)hydrazine carbodithioate (**3**)(Scheme 1, table 1). The structure of **3** was confirmed via spectral data and elemental analysis and chemical transformation.

The combination of solvents and long reaction time, costly chemicals makes this method environmentally hazardous. This provided the stimulus to synthesize these reactions using grinding technique. In grindstone technique, reaction occurs.

through generation of heat by grinding of substrate and reagent by mortar and pestle. Thus compound 1 was ground with 2 to give product identical in all aspects to that obtained by conventional method. IR spectrum of compound **3** revealed the presence of

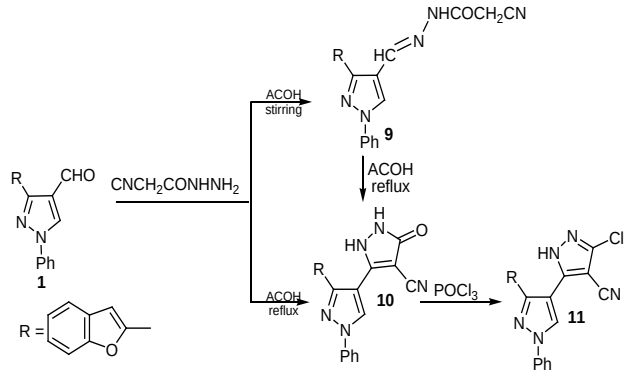
characteristic band for NH group and disappearance of carbonyl group. Its ^{1}H NMR spectrum recorded a wen signals at δ = 4.50 (s, 2H, SCH_2) and 13.37 ppm (s, 1H, NH).



Scheme 1: Reaction of 1 with hydrazonoyl halides

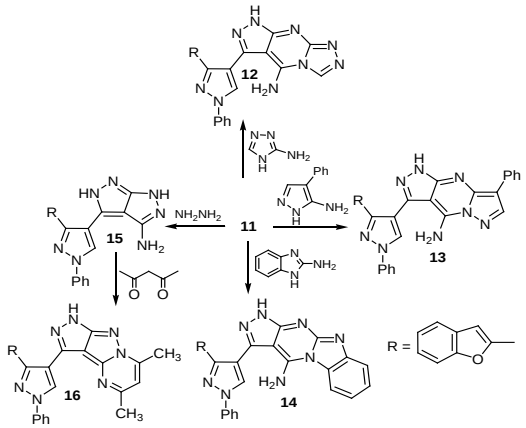
In addition, hydrazonoyl halides **4a-d** were reacted with benzyl hydrazinecarbodithioate derivative **3** in ethanol containing triethylamine to afford in each case one isolable product. The isolable products were assigned as 2-(5-substituted 3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(3-(benzofuran-2-yl)1-phenyl-1*H*-pyrazol-4-yl) methylene)hydrazines **8a-d** (Scheme 1, table 1) based on elemental analyses and spectral data (*see* experimental section). Compounds **8a-d** could be obtained in a better yield and short time by grinding the reactant together with two drops of triethylamine. The IR spectra of **8a-d** revealed absorption bands in the range of 1680-1735 cm^{-1}due to the carbonyl stretching vibrations while the absorption bands of the NH functions have been disappeared. The ^{1}H NMR spectrum of **8a** as an example, showed signals at δ: 1.42 (t, 3H, *J* = 7*Hz*, CH_2**CH_3**), 4.19 (q, 2H, *J* = 7*Hz*, **CH_2**CH_3). Furthermore, ^{13}C NMR spectrum of **8a** showed signals at δ: 14.5 (CH_3), 62.6 (CH_2), 105.9-150 (Ar-C), 167 ppm (C=O). In the light of the foregoing results, the mechanism outlined in Scheme 1 seems to be the most plausible pathway for the formation of **8** from the reaction of the **4** with **3**. The reaction involves initial formation of thiohydrazonate **6**, which undergoes intermolecular cyclization as soon as it is formed to yield the intermediate **7** or via 1,3-dipolar cycloaddition of nitrilimine **5** (prepared in situ from **4** with triethylamine) to the C=S double bond of **3**. Compound **7** was converted to **8** by elimination of benzyl mercaptan.

Moreover, Condensation of **1** with 2-cyanoacetohydrazide at room temperature afforded hydrazone derivative **9** which underwent heterocyclization to give pyrazoline derivative **10** either by boiling in acetic acid or grinding with KOH without solvent. Thus, alternative synthetic route for pyrazoline **10** could be obtained in one step by reaction of **1** with 2-cyanoacetohydrazide in boiling acetic acid (Scheme 2, table 1). The structures of **9** and **10** were established on the basis of elemental analyses and spectral data. IR spectrum of hydrazone **9** exhibited bands at 3128, 2256 cm^{-1} for NH and CN groups, respectively. Its ^{1}HNMR spectrum revealed a new signal at δ = 3.98 ppm corresponding to CH_2CN function. The mass spectrum of compound **9** showed a molecular ion peak m/z at 368 (M-1, 100%).



Scheme 2: Reaction of 1 with cyanoacidhydrazide

Heating of compound **10** with phosphorus oxychloride yielded 5-chloro pyrazole derivative **11** (Scheme 2). To examine the reactivity of chloro- and cyano- groups, compound **11** reacted with each of 2-aminotriazole, 4-phenyl-5-aminopyrazole and 2-amino benzimidazole in dioxane containing catalytic amount of triethylamine afforded compounds **12-14**, respectively (Scheme 3, table 1). The IR, ^{1}H NMR and mass spectra of **12-14** are in agreement with the proposed structures as shown in the experimental part.



Scheme 3: Reaction of 11 with amines

Further, the formation of these products was supported by alternative synthesis. Thus, grinding of chloro compound **11** and the appropriate amines in the presence of three drops of triethylamine gave product identical in all aspects (mp., mixed mp. and spectra) with the above mentioned method. In addition, the reactivity of compound **11** towards hydrazine hydrate was also investigated.

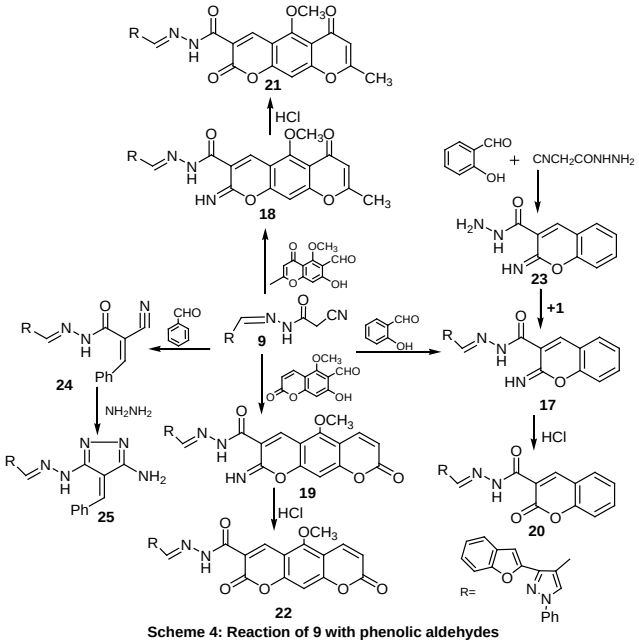
Thus, hydrazinolysis of compound **11** with hydrazine hydrate furnished novel 4-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-1,5-dihydropyrazolo [3,4-c]pyrazol-3-amine (**15**) which on reaction with acetyl acetone in acetic acid afforded 3-(3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-5,7-dimethyl-1H-pyrazolo[3',4':3,4] pyrazolo [1,5-a] pyrimidine (**16**) (Scheme 3, table 1). Compounds **15** and **16** could be obtained in excellent yield and short time by grinding method. The elemental analyses and spectral data revealed the required structures. The IR spectrum of **15** showed absorption bands at 3429, 3306 and 3190 cm^{-1} corresponding to NH and NH_2 functions, respectively.

The IR spectrum of **16** showed the absence of NH_2 function. Also, ^{1}H NMR spectrum of **16** indicated the presence of signals at δ = 2.30, 2.38 ppm due to $2CH_3$ groups. In addition, the structure of **16** was elucidated by its mass spectrum which revealed a molecular ion peak at m/z at 446 (M^++ 1, 100%).

Condensation of hydrazone **9** with phenolic aldehydes namely: salicylaldehyde, 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde, 7-hydroxy-5 methoxy- 2 - oxo-2*H*-chromene-6-carbaldehyde, under Knoevenagel reaction conditions afforded the corresponding imino coumarin derivatives **17-19**, respectively (Scheme 4, table 1). Structure of **17** was confirmed by elemental analysis, spectral data and alternative synthesis. Thus, 2-imino-2*H*-chromene-3-carbohydrazide (**23**) (which prepared via the reaction of salicylaldehyde with 2-cyanoacetohydrazide in ethanol containing piperidine) was reacted with aldehyde **1** to afford a product identical in all aspects (m. p., mixed m. p. and spectra) with **17** (Scheme 4).

Structures of newly synthesized compounds **17-19** were confirmed based on elemental analyses and spectral data. IR spectra of **17-19** showed the absence of cyano function and displayed a broad absorption bands in the region of 3385-3393 cm^{-1} characteristic to 2NH groups, in addition to a carbonyl absorption bands in the region of 1650-1660 cm^{-1}and the absorption bands in the region of 1602-1606 cm^{-1} for C=N. Their ^{1}H NMR spectra showed the absence of CH_2CN proton and revealed a signal at δ = 8.20- 8.53 ppm

corresponding to CH = N- group of hydrazone in addition to other signals due to the rest of the molecule.



Scheme 4: Reaction of 9 with phenolic aldehydes

The corresponding coumarin derivatives **20-22** were obtained through hydrolysis of imino coumarin **17-19** with 50% hydrochloric acid (Scheme 4, table 1). The Structure of compounds **20-22** were established through elemental analyses and spectral data beside alternative synthetic route.

Grinding of compound **9** and each of phenolic aldehydes together with two drops of piperidine gave product identical in all aspects (mp., mixed mp. and spectra) with **20-22** in a good yield (Scheme 4, table 1).

The IR spectra of compound **20** as an example displayed absorptions at 3335 and 1688 cm^{-1} for NH, C=O respectively. Additionally, the proton signals in ^1H NMR spectra of these compounds were observed at δ= 8.20-8.70 ppm and 10.20-13.50 ppm corresponding to CH=N group of hydrazone and NH protons respectively in addition to aromatic protons.

In contrasts, compound **9** reacts with benzaldehyde either by reflux in ethanol containing piperidine or by grinding without solvent to give **24** which reacted with hydrazine hydrate in boiling ethanol (or by grinding) to give **25** (Scheme 4). Spectral data (^1H, ^{13}C NMR, mass and elemental analysis) of all the newly synthesized compounds were in full agreement with the proposed structures. For example ^{13}C NMR spectrum of **25** showed signals at δ = 111.9-139.1 (Ar-C), 141.3, 160.8 ppm (C=N).

Table 1: Comparison between grinding and conventional method for synthesized compounds

Comp No	Grinding method		Conventional method	
	Time (min)	Yield (%)	Time (min)	Yield (%)
3	5	90	120	77
8a	7	92	120	75
8b	7	90	120	72
8c	7	90	120	71
8d	7	91	120	71
9	5	89	60	79
10	10	89	60	75
12	10	90	300	72
13	10	92	300	73
14	10	92	300	71
15	10	89	300	72
16	10	92	180	70
17	10	90	60	74
18	10	92	180	76
19	10	92	180	77
20	10	92	180	75
21	10	92	30	74
22	10	92	30	73
23	10	92	30	76
25	10	92	60	75
26	10	92	180	72

Biological activity

In vitro antibacterial activity data (Table 2) reveals that most the newly synthesized compounds showed slight to moderate activity in comparison to reference drug against the tested organisms.

Compounds **8b, 8d, 14, 18** and **23** showed intermediate to low activity against gram positive bacteria *Staphylococcus aureus*, while compound 13 showed no activity. Compounds **3, 8d, 23** showed low activities against gram positive bacteria *Bacillus subtilis* while compounds 8b, **13, 14** and **18** showed no activity.

All the tested compounds showed no activity against gram negative bacteria *Salmonella typhimurium* and *Escherichia coli.* From *in vitro* antifungal activity (Table 3) it was found that compound **3** showed intermediate activity towards *Candida albicans* while compound **13** showed low activity towards *Candida albicans and Aspergillus fumigatus.*

Table 2: Antibacterial activity data of tested compounds

Organism	Mean* of zone diameter, nearest whole mm.							
	Gram - positive bacteria				Gram - negative bacteria			
	S aureus (ATCC 25923)		*B subtilis* (ATCC 6635)		*S typhimurium* (ATCC 14028)		*E. coli* (ATCC 25922)	
Conc. Sample	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml
3	I	-	L	L	-	-	-	-
8b	I	L	-	-	-	-	-	-
8d	I	L	L	L	-	-	-	-
13	-	-	-	-	-	-	-	-
14	I	L	-	-	-	-	-	-
18	I	L	-	-	-	-	-	-
23	I	L	L	L	-	-		
Control #	35	26	35	25	36	28	38	27

* = Calculate from 3 values, – = No effect. ,L: Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of control., I: Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of control., H: High activity = Mean of zone diameter > 2/3 of mean zone diameter of control., #: Chloramphenicol in the case of Gram-positive bacteria, Cephalothin in the case of Gram-negative bacteria.

Table 3: Antifungal activity data of tested compounds

Organism	Mean* of zone diameter, nearest whole mm.			
	Yeasts and Fungi**			
	Candida albican (ATCC 10231)		*Aspergillus fumigatus*	
Conc. Sample	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml
3	I	I	-	-
8b	-	-	-	-
8d	-	-	-	-
13	L	L	L	L
14	-	-	-	-
18	-	-	-	-
23	-	-	L	L
Cycloheximide	**35**	**28**	**37**	**26**

* = Calculate from 3 values, ** = identified on the basis of routine cultural, morphological and microscopical characteristics, – = No effect, L: Low activity = Mean of zone diameter≤ 1/3 of mean zone diameter of control. , I: Intermediate activity = Mean of zone diameter≤ 2/3 of mean zon e diameter of control., H: High activity = Mean of zone diameter > 2/3 of mean zone diameter of control., #: Cycloheximide in the case of fungi.

CONCLUSION

In this article, we are reporting a facile, rapid, eco-friendly route with good yield for the synthesis of thiadiazole, coumarin and pyrazole derivatives just by grinding the reactants. Solvent-free approach is nonpolluting and does not employ any toxic materials. The investigation of antifungal and antibacterial screening data revealed that some of the tested compounds show moderate to low activities.

CONFLICT OF INTERESTS

Declared None

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