Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Synthesis, characterization, and biological studies of some novel pyrazole carboxamide, pyridazine and thienopyridazine derivatives

Ismail M. M. Othman & Abdel Haleem M. Hussein

To cite this article: Ismail M. M. Othman & Abdel Haleem M. Hussein (2019): Synthesis, characterization, and biological studies of some novel pyrazole carboxamide, pyridazine and thienopyridazine derivatives, Synthetic Communications, DOI: 10.1080/00397911.2019.1703002

To link to this article: https://doi.org/10.1080/00397911.2019.1703002

Published online: 26 Dec 2019.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1703002

Taylor & Francis
Taylor & Francis Group

Synthesis, characterization, and biological studies of some novel pyrazole carboxamide, pyridazine and thienopyridazine derivatives

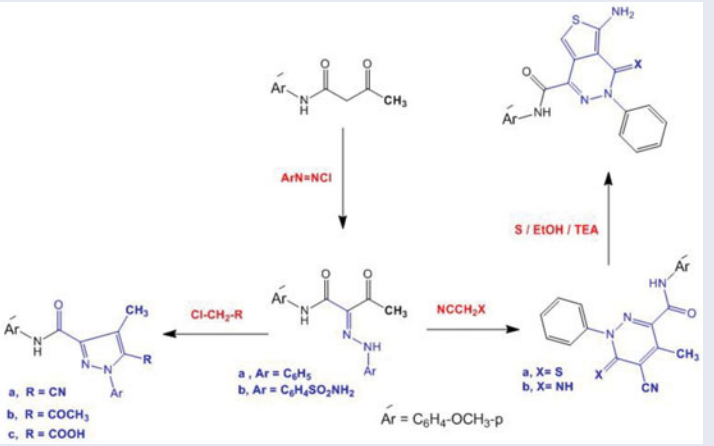
Ismail M. M. Othman and Abdel Haleem M. Hussein

Department of Chemistry, Faculty of Science, Al-Azhar University, Assiut, Egypt

ABSTRACT

The arylhydrazones **3a, b** were prepared and reacted with various reagents to yield the target compounds pyrazoles **6a–f**, 1,6-dihydropyridazine-3-carboxamide derivatives **9a,b** and thieno[3,4-*d*]pyridazine-1-carboxamide derivatives **10a,b**. The structures of the synthesized compounds were confirmed by various spectral data and elemental analyses. Furthermore, all target derivatives were tested for their antibacterial bioactivity against different types of Gram+ve and Gram-ve strains and for antifungal activity against two fungi micro-organisms by well diffusion method. Thus, the observed results showed that the 5-cyano-6-imino-N-(4-methoxyphenyl)-4-methyl-1-phenyl-1,6-dihydropyridazine-3-carboxamide (**9b**) displayed the best antimicrobial activity (with MIC values ranged from 0.49 ± 0.2 to 3.9 ± 0.6 μg/mL).

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 23 August 2019

KEYWORDS
Antimicrobial activities; pyrazoles; pyridazines; thieno[34-d]pyridazines

CONTACT Ismail M. M. Othman ismail201179@yahoo.com Department of Chemistry, Faculty of Science, Al-Azhar University, Assiut, Egypt.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Supplemental data for this article can be accessed on the publisher's website.

Introduction

Heterocyclic compounds are important key features in synthetic medicines and natural products due to their variation of possible substituents, less toxicity and large-efficiency[1–3]. Pyrazole derivatives are significant kinds of heterocyclic nitrogen compounds[4,5], which demonstrates a wide range of biological activities, such as anticancer[6,7], antimicrobial[8], antifungal[9], antitumor[10] and anti-inflammatory[11]. Some pyrazole derivatives based drugs belonging to various classes with different therapeutic activities (Fig. 1) have been successfully developed by various companies. The presence of the pyrazole moieties in varied compounds leads to different applications in diversified areas such as medicine, agriculture and technology. They are revealed as an antioxidant, inhibitors of protein glycation, anti-tuberculosis, antiviral and antibacterial agents[12,13]. In addition, heterocycles with carboxamide groups are constitute of a kind of compounds exhibiting extensive biological activities, such as antiproliferative[14], antibiofilm[15], plant growth regulation[16], They represent a valuable class of very numerous constructing blocks for the synthesis of bioactive compounds in agrochemical industry and pharmaceutical drug design. In the past few years, some succinate-dehydrogenase-inhibitor (SDHI) fungicides are possible in the market for effective therapy of vegetable crops and fruit, such as penflufen (which used for the therapy of a wide area of diseases) and sedaxane (Fig. 1). Pyridazine-based structures are widely found in biologically active compounds with anti-HAV agents[17], anticonvulsant[18], anti-Alzheimer's[19], anti-depressant[20], and so on. As an extension of our program in respect of synthesizing heterocyclic compounds particularly those with expected antimicrobial activity [21–24], we target to synthesize novel series of pyrazole, pyridazine, and thienopyridazine derivatives with the expectation that new biological agents might be discovered.

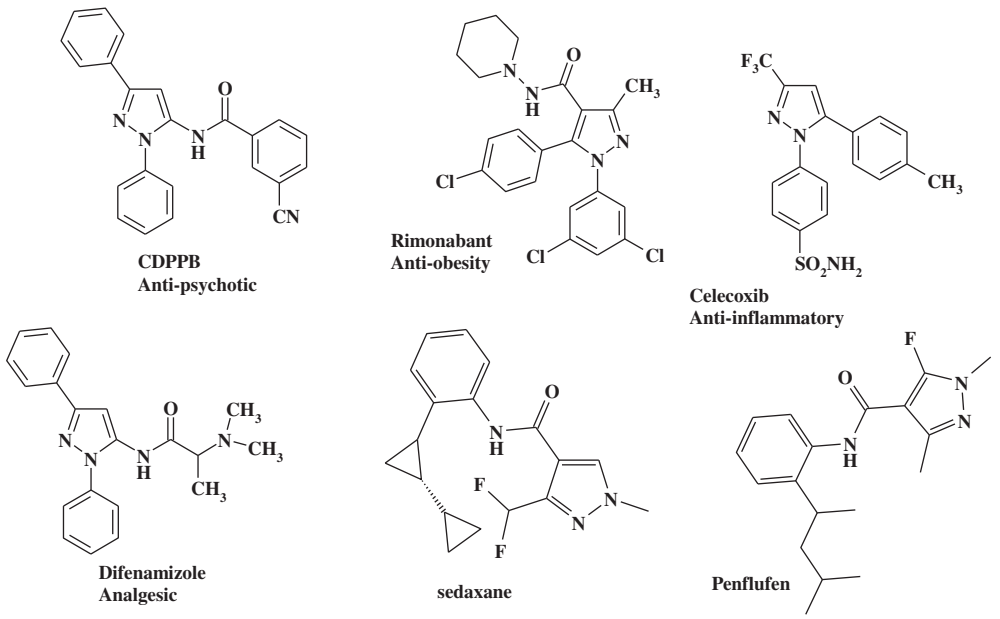
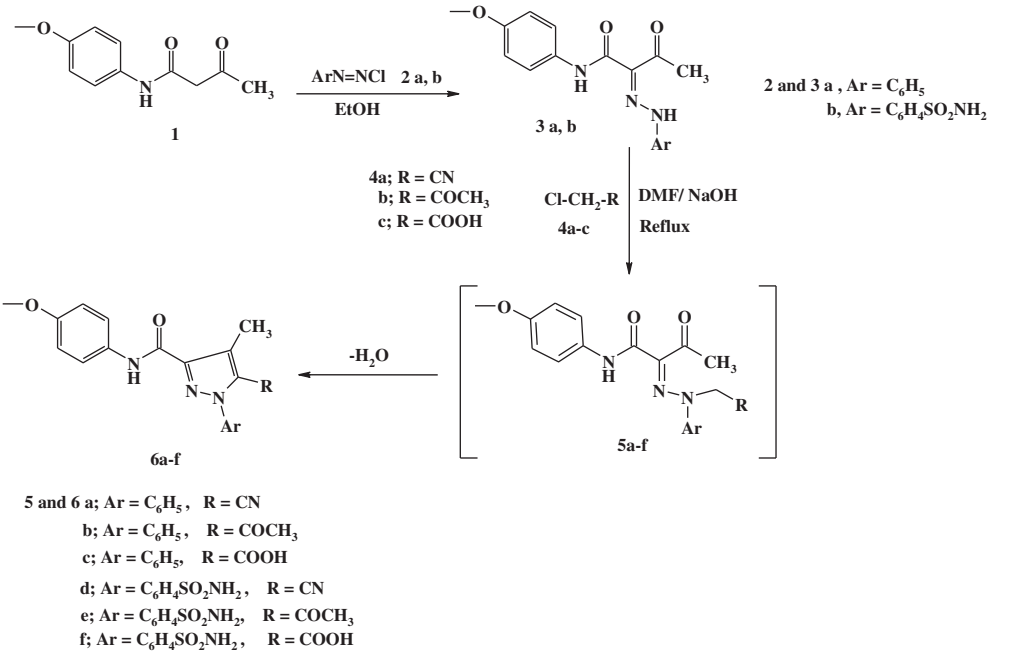


Figure 1. Pharmaceutical drugs containing pyrazole unit.

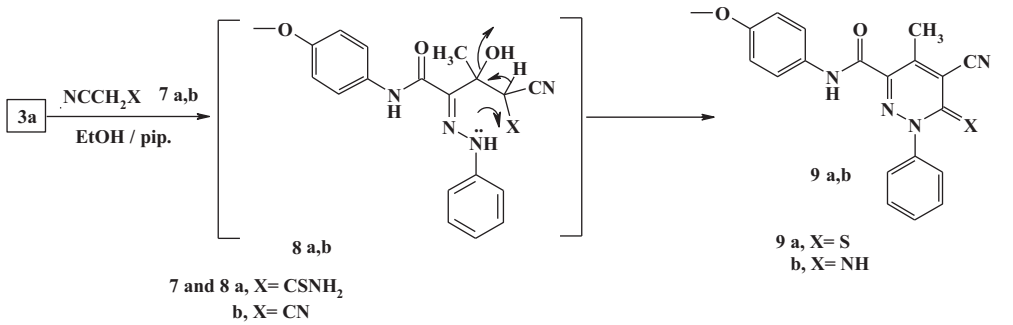
Results and discussion

Chemistry

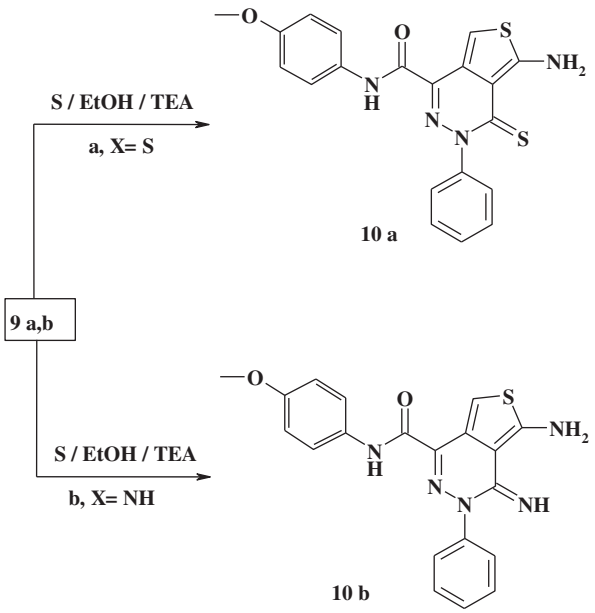
The structures of the prepared derivatives were showed in Schemes 1–3. Based on the synthetic strategies, it has been found that the coupling of *N*-(4-methoxyphenyl)-3-oxo-butanamide (**1**)[25], with diazotized aromatic amines **2a,b** in ethanol/AcONa yielded the hydrazono derivatives **3a,b** based on their spectral data, (Scheme 1). For instance, ^{1}H NMR spectrum of (**3a** in DMSO-d_6) displayed the presence of multiple signals at $\delta = 6.95–7.42$ ppm corresponding to aromatic protons and signals at $\delta = 9.11$ and 11.14 ppm corresponding to 2NH groups. The arylhydrazone derivatives **3** seem to be an interesting candidate for further chemical transformations. Thus, the arylhydrazones



Scheme 1. Synthesis of hydrazone and pyrazole derivatives



Scheme 2. Synthesis of pyridazine derivatives



Scheme 3. Synthesis of thienopyridazine derivatives

3a,b were treated with halo compounds **4a–c** to yield pyrazole carboxamide products. So, structures **3a**,**b** were reacted with equimolecular amount of chloroacetonitrile (**4a**), chloroacetone (**4 b**) and chloroacetic acid (**4c**) in the presence of few plates of sodium hydroxide and dimethylformamide (DMF) under reflux for 6 hours to yield the pyrazole derivatives **6a–f**. Confirmations of compounds **6a–f** were based on its compatible spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR). The IR spectrum of compound **6a** exhibited the appearance of absorption bands due to the NH, CN and CO functional groups at υ 3372, 2207 and 1663 cm^{-1}, respectively. While its ^{1}H NMR spectrum indicated singlet signal at δ 10.65 ppm assigned to NH amidic group and the disappearance of any signal corresponding to NH proton of hydrazo group at high downfield beside the other protons in their proper positions (Scheme 1 and Experimental part). Moreover, ^{13}C NMR of the pyrazole carboxamide **6a** illustrated signal at δ 114.1 ppm characterized to the carbon of CN group, in addition, to signal at δ 163.8 ppm attributed to the carbon of CO group.

Construction of **6** was carried via the nucleophilic attack of NH hydrazo group of **3** to the halogen compound **4** to give the intermediate **5** which cyclized through the nucleophilic attack of active methylene moiety in **5** to the carbon of the acetyl group to yield the reaction products **6a–f** via removal of H_2O molecule. Furthermore, the obtained arylhydrazones were utilized as starting materials for the synthesis of some novel pyridazine and thienopyridazine derivatives. Thus, the reaction of arylhydrazone **3a** with cyanothioacetamide (**7a**) or malononitrile (**7b**) in ethanol/piperidine under reflux yielded the corresponding compounds dihydropyridazine-3-carboxamide derivatives **9a,b**. (Scheme 2).

The structures of **9a,b** were confirmed via analysis of their spectral studies. The IR spectra of **9a**, taken as a typical example, illustrate absorption bands at 3343, 2203, and

1661 cm^{-1} corresponding to NH, CN, and CO groups, respectively. While its ^{1}H NMR spectrum indicated signals at δ 2.71, 3.83 and 10,15 corresponding to $2CH_3$ and NH protons in addition to aromatic protons at δ 7.07–8.19. Also, ^{13}C NMR of the structure revealed signals at 113.1 ppm (CN), 163.5 ppm (C=O), 182.3 ppm (C=S), in addition to all signals assigned to carbons of sp^2 in the molecule. Formation of the iminopyridazine derivative **9b** was proposed to proceed by condensation of the methylene group in compound **7b** with carbonyl of acetyl group in **3a** to yield the non-isolated intermediate **8b** which cyclized through nucleophilic attack of NH group to CN group affording the iminopyidazine derivative **9 b**, (Scheme 2). The pyridazine carboxamide derivative**s 9a,b** were utilized as starting material to obtain some fused azines[26]. Thus, the pyridazines **9a,b** were reacted with elemental sulfur in boiling ethanol/triethylamine to afford the dihydrothieno[3,4-*d*]pyridazine carboxamide derivatives **10a,b**. The spectral and elemental analysis data are in accordance with the assigned compounds **10a,b**. For instance, the IR spectra of **10a** displayed the absence of the absorption band assigned to the CN function group and the appearance of an absorption band corresponding to the NH_2 groups at υ 3375, 3229 cm^{-1}. ^{1}H NMR spectrum (DMSO-d_6) displayed signals that is in accordance with the expected structure at δ 3.82, 5.12 ppm attributed to the OCH_3 and NH_2 protons and multiple signals in the region of δ 6.97–7.52 ppm attributed to aromatic protons in addition to NH proton at δ 10.21. ^{13}C NMR spectra of the dihydrothieno[3,4-*d*]pyridazine derivative **10a** displayed two signals at 163.3 and 172.1 ppm due to CONH and CS groups, (Scheme 3 and Experimental part).

Antimicrobial testing

As clarified in Table 1, the newly targeted structures examined exhibited in vitro antibacterial against *Streptococcus pneumonia*, *Bacillus subtilis, Pseudomonas aeruginosa*, *Escherichia coli,* and antifungal against *Aspergillus fumigatus and Candida*

Table 1. Diameter of inhibition zone (mm) of the synthesized compounds at 1 mg/mL.

	Mean diameter of inhibition zone (Mean ± SEM) (mm)					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
Compounds	*S. pneumoniae* RCMB 010010	*B. subtilis* RCMB 010067	*P. aeruginosa* RCMB 010043	*E. coli* RCMB 010052	*A. fumigatus* RCMB 002568	*C. albicans* RCMB 005036
3a	12.8 ± 0.4	NA	NA	NA	10.3 ± 1.5	NA
3b	18.5 ± 0.7	20.3 ± 0.5	26.3 ± 0.1	11.8 ± 0.5	16.4 ± 1.5	14.2 ± 1.2
6a	NA	20.1 ± 0.6	15.1 ± 0.7	NA	17.7 ± 0.5	NA
6b	NA	NA	NA	NA	NA	NA
6c	NA	NA	NA	NA	NA	NA
6d	26.4 ± 0.5	23.8 ± 1.3	19.2 ± 0.5	15.3 ± 1.3	22.6 ± 0.5	17.5 ± 0.2
6e	23.1 ± 0.8	18.1 ± 0.6	17.2 ± 1.5	14.8 ± 0.1	21.2 ± 0.4	11.4 ± 0.3
6f	27.2 ± 0.4	24.1 ± 0.5	22.6 ± 0.5	21.2 ± 1.3	18.7 ± 1.5	15.5 ± 0.2
9a	13.4 ± 0.6	NA	12.3 ± 0.4	16.1 ± 0.5	14.6 ± 1.3	NA
9b	28.6 ± 0.5	25.7 ± 0.2	23.5 ± 1.2	24.1 ± 0.1	20.2 ± 1.2	26.3 ± 0.5
10a	NA	NA	NA	NA	NA	NA
10b	23.5 ± 0.7	27.7 ± 0.3	20.2 ± 1.5	19.7 ± 0.7	12.2 ± 1.3	13.1 ± 0.7
Ketoconazole	–	–	–	–	23.7 ± 1.1	25.4 ± 0.1
Gentamycin	23.8 ± 0.7	26.4 ± 0.5	19.7 ± 0.6	24.9 ± 1.5	–	–

NA: No activity under the screening conditions; –: Not tested; SEM: standard error mean; each value is the mean of 3 values.

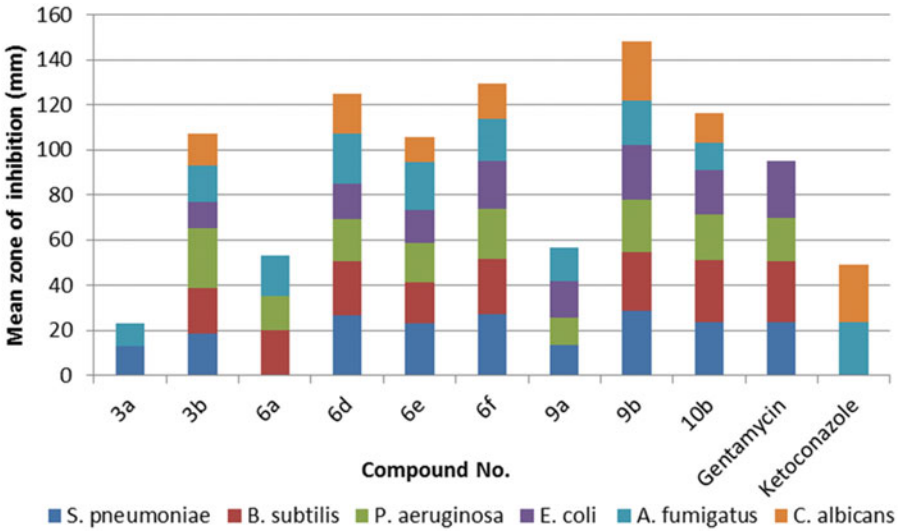


Figure 2. Comparison of the biological activity of the newly target compounds.

albicans. A solution of the target derivatives in concentration 1 mg/mL were tested against the various organisms and reported as inhibition zone diameter in mm (agar well diffusion procedure) (Table 1 and Fig. 2). Derivatives **3a**, **3b**, **6a**, **6d**, **6e**, **6f**, **9a**, **9b** and **10b** illustrated bioactivity ranging from reasonable to excellent against all organisms strains. However, compound **9b** showed the highest activity against all microorganism's strains used in this investigation. In addition, structure **9b** displayed nearly equipotent inhibition region as the standard drugs used for against organisms, followed by compounds, **6f**, **10b**, **6d**, **6e**, **3b**, **9a**, **6a** and **3a**, respectively. On the other hand, the 3-oxo-2-(2-phenylhydrazono)butanamide derivative **3a** displayed weak bioactivity on both of *S. pneumonia* and *A. fumigates*, whereas both of compounds **6b,c** and **10a** had no pathogens activities. Moreover, the most bioactive structures **3b**, **6d**, **6e**, **6f**, **9b** and **10b** were inspected for the determination of the minimum inhibitory concentration (MIC). Compound **9b** illustrated the best MIC values ranged from 0.49 ± 0.2 to 3.9 ± 0.6 µg/mL, followed by **6f**, **10b**, **6d**, **6e** and **3b** (MIC 0.98 ± 0.1–250 ± 0.6 µg/mL) (Table 2).

Antimicrobial activity

All biological strains were received from the culture collection of the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo, Egypt. All target derivatives were tested in-vitro against to various kinds of bacteria, Gram-positive bacteria (*Streptococcus pneumoniae* and *Bacillus subtilis*) and Gram-ve bacteria (*Pseudomonas aeruginosa* strain and *Escherichia coli* strain) and against *Aspergillus fumigatus* strain, *Candida albicans* strain for their antifungal activity, respectively. The standard drugs of gentamycin and ketoconazole were used as examples of antibacterial and antifungal activity. The diameter of the inhibition zone (mm) was measured for the antimicrobial bioactivity using the diffusion technique[27]. The proper target structures were further tested to estimate their

Table 2. Minimum inhibitory concentration (MIC) (μg/mL) of the most bioactivity derivatives.

	MIC (Mean ± SEM) (μg/mL)					
	Gram + ve bacteria		Gram-ve bacteria		Fungi	
Compd.	*S. pneumoniae* RCMB 010010	*B. subtilis* RCMB 010067	*P. aeruginosa* RCMB 010043	*E. coli* RCMB 010052	*A. fumigatus* RCMB 002568	*C. albicans* RCMB 005036
3b	7.81 ± 0.2	3.9 ± 0.03	0.98 ± 0.1	250 ± 0.6	15.63 ± 0.2	125 ± 0.05
6d	0.98 ± 0.2	1.95 ± 0.5	3.9 ± 0.2	62.5 ± 0.1	1.95 ± 0.3	15.63 ± 0.3
6e	0.98 ± 0.03	7.81 ± 0.2	15.63 ± 0.4	125 ± 0.3	3.9 ± 0.2	250 ± 0.05
6f	0.49 ± 0.4	0.98 ± 0.1	3.9 ± 0.3	3.9 ± 0.1	7.81 ± 0.3	62.5 ± 0. 5
9b	0.49 ± 0.2	0.98 ± 0.01	1.95 ± 0.01	0.98 ± 0.5	3.9 ± 0.6	0.98 ± 0.6
10b	0.98 ± 0.1	0.49 ± 0.3	3.9 ± 0.01	3.9 ± 0.3	250 ± 0.1	125 ± 0.2
Ketoconazole	–	–	–	–	1.95 ± 0.3	0.98 ± 0.1
Gentamycin	–	–	3.9 ± 0.6	0.98 ± 1.03	–	–

–: Not tested; NA: No activity under the screening conditions; SEM: mean of the standard error; each value is the mean of 3 values.

antimicrobial activity expressed in terms of minimum inhibitory concentration (MIC) using the modified agar well diffusion method[27].

Conclusion

3-Oxobutanamide derivative **1** was used to synthesize new valuable heterocycles targeting to excess their synthetic potential. Moreover, arylhydrazones **3a,b** were used as a valuable scaffold to build different heterocyclic rings through simple and synthetic strategies reactions. Finally, on the inspection of newly-synthesized structures for their antimicrobial bioactivity against selected pathogens strains, we noted that pyridazine carboxamide derivative **9b** displayed an excellent activity among all microorganism's strains used in this investigation.

Experimental

Melting points were determined with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded on a Pye-Unicam Sp-100 spectrophotometer using KBr wafer technique. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (100 MHz) measurements were executed using Varian-400 MHz spectrometer, and chemical shifts were expressed in δ (ppm) relative to TMS (in DMSO-d_6 as solvent) as the internal standard at the Microanalytical center, Cairo and Assiut University. The elemental analyses were executed on Perkin-Elmer 2400 elemental analyzer, and the values found were within ±0.3% of the theoretical. Preparative and analytical TLC were executed on silica gel plates (Fluka 70643-50EA. Sigma-Aldrich, Germany) using UV light. All reactions were carried out under an air atmosphere.

General procedure for preparation of compounds 3a,b

To a cold solution of *N*-(4-methoxyphenyl)-3-oxobutanamide (**1**) (2.07 g, 10 mmol) and sodium acetate (2 g) in ethanol (40 mL), the appropriate diazonium chlorides **2a,b** (prepared from (0.91 mL and 1.72 g, 10 mmol) of amines and the appropriate quantities of

HCl 4.00 mL and $NaNO_2$ (0.69 g, 10 mmol)) were added. The addition was carried out portion-wise with stirring at 0–5 °C over a period of 15 min. After complete addition, the reaction mixture was stirred further for 1 h. The precipitated solid was collected by filtration, washed with water, dried, and finally recrystallized from the proper solvent to afford the corresponding coupling products **3a,b**.

N-(4-Methoxyphenyl)-3-oxo-2-(2-phenylhydrazono)butanamide (3a)

It was obtained as red crystals from ethanol; yield (2.7 g, 90%), mp. 180–181 °C; IR (KBr) ν cm^{-1} 3247, 3185 (2NH), 3051 (CH-arom.), 2980 (CH-aliph.), 1686, 1662 (2C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.48 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.95–7.42 (m, 9H, Ar–H), 9.11 (s, 1H, NH), 11.14 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 25.8, 55.2, 113.1, 114.0, 122.6, 123.7, 127.1, 129.7, 132.3, 143.0, 157.2, 164.3, 190.5. Anal. Calc. For $C_{17}H_{17}N_3O_3$ (311.34): C, 65.58; H, 5.50; N, 13.50%.Found: C, 65.80; H, 5.71; N, 13.73%.

N-(4-Methoxyphenyl)-3-oxo-2-(2-(4-sulfamoylphenyl)hydrazono)butanamide (3b)

It was obtained as yellow crystals from ethanol; yield (3.3 g, 89%), mp. 193–194 °C; IR (KBr) ν cm^{-1} 3433, 3325 (NH_2), 3252, 3147 (2NH), 3058 (CH-arom.), 2974 (CH-aliph.), 1691, 1665 (2C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 7.31–7.89 (m, 10H, Ar–H + NH_2), 10.17 (s, 1H, NH), 11.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 27.1, 54.6, 114.5, 117.0, 122.2, 128.3, 129.7, 130.1, 132.3, 145.4, 157.5, 164.8, 191.11. Anal. Calc. for $C_{17}H_{18}N_4O_5S$ (390.41): C, 52.30; H, 4.65; N, 14.35; S, 8.21%.Found: C, 52.54; H, 4.86; N, 14.57; S, 8.43%.

Full experimental section and spectral data can be presented in the Supplementary Information.

References

[1] Zhai, Z. W.; Yang, M. Y.; Sun, Z. H.; Liu, X. H.; Weng, J. Q.; Tan, C. X. Facile and Efficient Synthesis of Novel 1,2,3-Thiadiazole Derivatives Using Microwave Irradiation. *J. Chem. Res.* **2015**, *39*, 340–342. DOI: 10.3184/174751915X14326308763971.

[2] Zhang, L. J.; Yang, M. Y.; Sun, Z. H.; Tan, C. X.; Weng, J. Q.; Wu, H. K.; Liu, X. H. Synthesis and Antifungal Activity of 1,3,4-Thiadiazole Derivatives Containing Pyridine Group. *LDDD.* **2014**, *11*, 1107–1111. DOI: 10.2174/15701808116661406102127 31.

[3] Zhang, L. J.; Yang, M. Y.; Hu, B. Z.; Sun, Z. H.; Liu, X. H.; Weng, J. Q.; Tan, C. X. Microwave-Assisted Synthesis of Novel 8-Chloro-[1,2,4]Triazolo[4,3-a]Pyridinederivatives. *Turk. J. Chem.* **2015**, *39*, 867–873. DOI: 10.3906/kim-1408-78.

[4] Lim, J.; Altman, M. D.; Baker, J.; Brubaker, J. D.; Chen, H.; Chen, Y.; Kleinschek, M. A.; Li, C.; Liu, D.; Maclean, J. K. F.; et al. Identification of N-(1H-Pyrazol-4-yl)Carboxamide Inhibitors of Interleukin-1 Receptor Associated Kinase 4: Bicyclic Core Modifications. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5384–5388. DOI: 10.1016/j.bmcl.2015.09.028.

[5] Bavetsias, V.; Pérez-Fuertes, Y.; McIntyre, P. J.; Atrash, B.; Kosmopoulou, M.; O'Fee, L.; Burke, R.; Sun, C.; Faisal, A.; Bush, K.; et al. 7-(Pyrazol-4-yl)-3H-Imidazo[4,5-b]Pyridine-Based Derivatives for Kinase Inhibition: Co-Crystallisation Studies with Aurora-a Reveal Distinct Differences in the Orientation of the Pyrazole N1-Substituent. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4203–4209. DOI: 10.1016/j.bmcl.2015.08.003.

[6] Abdelgawad, N.; Ismail, M.F.; Hekal, M.H.; Marzouk, M.I. Design, Synthesis, and Evaluation of Some Novel Heterocycles Bearing Pyrazole Moiety as Potential Anticancer Agents. *J. Heterocyclic Chem.* **2019**, *56*, 1771–1779. DOI: 10.1002/jhet.3544.

[7] Nossier, E. S.; Abd El-Karim, S. S.; Khalifa, N. M., El-Sayed, A. S.; Hassan, E. S. I.; El-Hallouty, S. M. Kinase Inhibitory Activities and Molecular Docking of a Novel Series of Anticancer Pyrazole Derivatives. *Molecules.* **2018**, *23*, 3074–3091. DOI: 10.3390/molecules.23123074.

[8] Viveka, S.; Madhu, L. N.; Nagaraja, G. K. Synthesis of New Pyrazole Derivatives via Multicomponent Reaction and Evaluation of Their Antimicrobial and Antioxidant Activities. *Monatsh Chem.* **2015**, *146*, 1547–1555. DOI: 10.1007/s00706-015-1428-5.

[9] Sowdari, J.; Gudi, Y.; Donthamsetty, S. V.; Venkatapuram, P.; Adivireddy, P. Green Approach for the Synthesis of a New Class of Diamidomethanelinked Benzazolyl Pyrazoles and Evaluation as Antifungals. *J. Heterocyclic Chem.* **2019**, *56*, 2080–2089. DOI: 10.1002/jhet.3569.

[10] Ismail, M. M.; Soliman, D. H.; Farrag, A. M.; Sabour, R. Synthesis, Antitumor Activity, Pharmacophore Modelling and QSAR Studies of Novel Pyrazoles and Pyrazolo[1,5-*a*]Pyrimidines against Breast Adenocarcinoma MCF-7 Cell Line. *Int. J. Pharm. Pharm. Sci.* **2016**, *8*, 434–442.

[11] Surendra, K. R.; Arif, I. A.; Ahamed, A.; Idhayadhulla, A. Anti-Inflammatory and Antimicrobial Activities of Novel Pyrazole Analogues. *Saudi J. Biol. Sci.* **2016**, *23*, 614–620. DOI: 10.1016/j.sjbs.2015.07.005.

[12] Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. Simón-Fuentes, from 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. *Chem. Rev.* **2011**, *111*, 6984–7034. DOI: 10.1021/cr2000459.

[13] Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman, S. Biologically Active Pyrazole Derivatives. *New J. Chem.* **2017**, *41*, 16–41. DOI: 10.1039/c6nj03181a.

[14] Wang, Y. H.; Goto, M.; Wang, L. T.; Hsieh, K. Y.; Morris-Natschke, S. L.; Tang, G. H.; Long, C. L.; Lee, K. H. Multidrug Resistance-Selective Antiproliferative Activity of Piper Amide Alkaloids and Synthetic Analogues. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4818–4821. DOI: 10.1016/j.bmcl.2014.08.063.

[15] Reddy, K. R.; Poornachandra, Y.; Dev, G. J.; Mallareddy, G.; Nanubolu, J. B.; Kumar, C. G.; Narsaiah, B. Synthesis of Novel Amide Functionalized 2H-Chromene Derivatives by Ritter Amidation of Primary Alcohol Using HBF4 Center Dot OEt2 as a Mild and Versatile Reagent and Evaluation of Their Antimicrobial and anti-Biofilm Activities. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2943–2947. DOI: 10.1016/j.bmcl.2015.05.041.

[16] Yan, S. L.; Yang, M. Y.; Sun, Z. H.; Min, L. J.; Tan, C.X.; Weng, J. Q.; Wu, H. K.; Liu, X. H. Synthesis and Antifungal Activity of 1,2,3-Thiadiazole Derivatives Containing 1,3,4-Thiadiazole Moiety. *LDDD.* **2014**, *11*, 940–943. DOI: 10.2174/1570180811666140423222141.

[17] Flefel, E. M.; Tantawy, W. A.; El-Sofany, W. I.; El-Shahat, M.; El-Sayed, A. A.; Abd-Elshafy, D. N. Synthesis of Some New Pyridazine Derivatives for Anti-HAV Evaluation. *Molecules*. **2017**, *22*, 148–162. DOI: 10.3390/molecules22010148.

[18] Sharma, B.; Verma, A.; Sharma, U. K.; Prajapati, S. Efficient Synthesis, Anticonvulsant and Muscle Relaxant Activities of New 2-((5-Amino-1,3,4-Thiadiazol-2-yl)Methyl)-6-Phenyl-4,5-Dihydropyridazin-3(2H)-One Derivatives. *Med. Chem. Res.* **2014**, *23*, 146–157. DOI: 10.1007/s00044-013-0618-0.

[19] Lin, H.; Fang, H.; Wang, J.; Meng, Q.; Dai, X.; Wu, S.; Luo, J.; Pu, D.; Chen, L.; Minick, D.; et al. Discovery of a Novel 2,3,11,11a-Tetrahydro-1H-Pyrazino [1,2-b]Isoquinoline-1,4(6H)-Dione Series Promoting Neurogenesis of Human Neural Progenitor Cells. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3748–3753. DOI: 10.1016/j.bmcl.2015.05.084.

[20] Boukharsa, Y.; Meddah, B.; Tiendrebeogo, R. Y.; Ibrahimi, A.; Taoufik, J.; Cherrah, Y.; Benom-Ar, A.; Faouzi, M. E. A.; Ansar, M. H. Synthesis and Antidepressant Activity of 5-(Benzo[b]Furan-2-Ylmethyl)-6- Methylpyridazin-3(2H)-One Derivatives. *Med. Chem. Res.* **2016**, *25*, 494–500. DOI: 10.1007/s00044-015-1490-x.

[21] Gad-Elkareem, M. A. M.; Othman, I. M. M. Synthesis, Reactions and Biological Evaluation of Novel 7-Thioxopyrido[2,3-d][1,2,3]Triazine Derivatives Bearing Sulfonamide Moiety. *Inter. J. Adv. Res.* **2016**, *4*, 1689–1700.

[22] Hussein, A. M.; Khames, A. A.; El-Adasy, A. A. A.; Gad-Elkareem, M. A. M.; Othman, I. M. M. β-Oxanilide in Heterocyclic Synthesis: Synthesis of Pyridazine, Pyrazole and Triazine Derivatives Carrying Sulfonamide and Antipyrine Moieties. *Int. J. Pharma. Sci.* **2015**, *5*, 864–874.

[23] Gad-Elkareem, M. A. M.; Othman, I. M. M. Synthesis and Antimicrobial Evaluation of Some New Thienopyrazoles, Pyrazolothienopyridines and Pyrazolothienopyrimidines via Gewald Reaction. *Int. J. Pharma. Sci.* **2017**, *7*, 1808–1816.

[24] Hussein, A. M.; El-Adasy, A. A. A.; Khames, A. A.; Atalla, A. A.; Abdel-Rady, M. 3-Oxobutanamides in Heterocyclic Synthesis, Synthesis Approaches for New Pyridines, Pyrimidines and their Fused Derivatives. *Chemistry Select.* **2017**, *2*, 1625–1629. DOI: 10.1002/slct.201601424.

[25] Wang, J.; Li, H.; Zhang, D.; Huang, P.; Wang, Z.; Zhang, R.; Liang, Y.; Dong, D. Divergent Synthesis of α,α-Dihaloamides Through α,α-Dihalogenation of β-Oxo Amides by Using *N*-Halosuccinimides. *Eur. J. Org. Chem.* **2013**, *2013*, 5376–5380. DOI: 10.1002/ejoc.201300341.

[26] Al-Mousawi, S. M.; El-Apasery, M. A.; Mahmoud, H. M. Disperse Dyes Based on Aminothiophenes: Their Dyeing Applications on Polyester Fabrics and Their Antimicrobial Activity. *Molecules*. **2013**, *18*, 7081–7092. DOI: 10.3390/molecules18067081.

[27] Ibrahim, H. S.; Eldehna, W. M.; Abdel-Aziz, H. A.; Elaasser, M. M.; Abdel-Aziz, M. M. Improvement of Antibacterial Activity of Some Sulfa Drugs through Linkage to Certain Phthalazin-1(2H)-One Scaffolds. *Eur. J. Med. Chem.* **2014**, *85*, 480–486. DOI: 10.1016/j.ejmech.2014.08.016.