SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF PHENYLPYRAZOLE DERIVATIVES

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ABSTRACT

The narrow antibacterial spectrum of phenylthiazole antibiotics was expanded by replacing the central thiazole with a pyrazole ring while maintaining its other pharmacophoric features. The most promising derivative, compound **10**, was moderate potent against MDR-Gram-positive clinical isolates, including vancomycin- and linezolid-resistant MRSA, with a minimum inhibitory concentration (MIC) value 8 g/mL. Moreover, compound **10** was promising against highly pathogenic carbapenem-resistant strains, such as *Acinetobacter baumannii, Klebsiella pneumoniae* and *E. coli.* In addition to the notable biofilm inhibition activity, compound **10** outperformed both vancomycin and kanamycin in reducing the intracellular burden of both Gram-positive and Gram-negative pathogenic bacteria. Compound **10** cleared 90% of intracellular MRSA and 98% of *Salmonella enteritidis* at 2× the MIC.

Keywords: Phenylpyrazole, Broad spectrum, Phenylthiazole, Linezolid, Carbapenem-resistant enterobacteriaceae.

INTRODUCTION

Antibiotics are the ‘wonder drugs’ to combat microbes cause different types of infections. Before the discovery of these agents, people were suffered from various kinds of infections, which often reached epidemic proportions and have cost the lives of millions of people till the discovery of the healing effects of (antibiotic producing) molds, this time was known as the *pre-antibiotic era*.(Zimdahl 2015) after discovery of antibiotics, the *antibiotic era* show multiple varieties of antibiotics which have not only been used for therapeutic purposes but practiced prophylactically across other industries such as agriculture and animal husbandry.(Begemann, Perkins et al. 2018),(Martin, Thottathil et al. 2015) This expanded use lead to rapid overspreading of resistance. In addition, Fleming was one of the early cautioned about the emergence of penicillin-resistance by defects in dose or duration of treatment, which was the warning indicator for the beginning of the *antibiotic resistance-emergence* era.(Aminov 2010)

In the last decades, antibiotic resistance has been declared to be a “global public health concern” by numerous important organizations, as the Centers for Disease Control and Prevention (CDC), World Economic Forum and the World Health Organization (WHO).(Michael, Dominey-Howes et al. 2014),(Spellberg,

Srinivasan et al. 2016) The World Health Assembly requested WHO to propose a global action plan to fight the antibiotic resistance problem.(Hoffman, Caleo et al. 2015) In the UK, people voted for a government-sponsored prize of £10 million (Longitude Prize challenge) to create novel solutions in combating antibiotic resistance.(Payne, Miller et al. 2015),(Luepke and Mohr III 2017) In America, by 2015, the US President's Council of Advisors on Science and Technology ordered the National Security Council to draft a comprehensive national action plan to tackle antibiotic resistance.(Luepke and Mohr III 2017),(Ventola 2015)

chemistry

All biologically tested compounds are with purity of 95% or more. ^{1}H NMR spectra were run at 400 MHz and ^{13}C NMR spectra were determined at 100 MHz in deuterated chloroform ($CDCl_3$), or dimethyl sulfoxide (DMSO-d_6) on a Varian Mercury VX-400 NMR spectrometer. Chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Chemical shifts were calibrated relative to those of the solvents. Flash chromatography was performed on 230-400 mesh silica. The progress of reactions was monitored with Merck silica gel IB2-F plates (0.25 mm thickness). The infrared spectra were recorded in potassium bromide disks on pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. Mass spectra were recorded at 70 eV. High-resolution mass spectra for all ionization techniques were obtained from a FinniganMAT XL95. Melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. All yields reported refer to isolated yields. (4-Iodophenyl)hydrazine (**2**)(BROWN, BRADSHER et al. 1959) and 1-(1-(4-iodophenyl)-5-methyl-1*H*-pyrazol-4-yl)ethanone (**3**)(Wang, Li et al. 2015) were prepared as reported.

Experimental

1-(5-Methyl-1-(4-substituted alkenyl) phenyl)1*H*pyrazol-4-yl)ethanone (4 -8).

General procedure:

To DMF (10 mL) in a 75-mL sealed tube, compound **3** (300 mg, 0.9 mmol), appropriate alkenes (1.8 mmol, 2 equiv.), potassium carbonate (380 mg, 2.7 mmol). After the reaction mixture was purged with dry nitrogen gas for 15 minutes, palladium acetate (41 mg, 20% mol) was added. The sealed tube was then placed in an oil bath and stirred at 80 ^{o}C for 24 hours. After cooling to room temperature, the reaction mixture was passed through celite, followed by ethylacetate (2×50 mL) and dried over magnesium sulphate. The organic materials were then concentrated under reduced pressure. The crude materials were purified and washed via silica gel flash column chromatography using hexane-ethylacetate (7:3). Yields, physical properties, and spectral data of isolated purified products are listed below:

1-(1-(4-(cyclopentylidenemethyl)phenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one (4). Yellow oil (220 mg, 85%). ^{1}H NMR (DMSO-d_6) δ: 8.22 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 11.6 Hz, 1H), 2.57 (s, 3H), 2.51 (t, J = 5.4 Hz, 4H), 2.44 (s, 3H), 1.73-1.69 (m, 4H); MS (*m*\z); 280 (M^{+}, 77.6%).

1-(1-(4-(2-cyclohexylvinyl)phenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one (5). brown oil (240 mg, 86%). ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 6.39 (dd, *J* = 15.3, 6.4 Hz, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.18-2.12 (m, 1H), 1.81-1.17 (m, 10H); ^{13}C NMR (DMSO-d_6) δ: 193.4, 142.6, 138.5, 138.2, 137.1, 126.9, 126.5, 125.8, 125.6, 121.1, 32.8, 29.1, 26.6, 26.1, 25.9, 12.3; MS (*m\z*); 308 (M^+, 19.23%).

1-(1-(4-(3-cyclopentylprop-1-en-1-yl)phenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one (6). Brown oil (264 mg, 93%). ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.19 (d, *J* = 12.4 Hz, 1H), 6.05 (dd, *J* = 16.3, 7.4 Hz, 1H), 3.05 (t, *J* = 7.9 Hz, 2H), 2.51 (s, 3H), 2.44 (s, 3H), 2.12-1.63 (m, 9H); MS (*m\z*); 308 (M^+, 100%).

1-(1-(4-(cyclohept-1-en-1-yl)phenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one (7). Yellow oil (215 mg, 80%). ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.30 (d, *J* = 6.8 Hz, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.39-1.54 (m, 10H); MS (*m\z*); 294 (M^+, 32.29%).

1-(1-(4-(cyclooct-1-en-1-yl)phenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one (8). yellow oil (230 mg, 82%). ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 6.41 (d, *J* = 16.1 Hz, 1H) 2.47 (s, 3H), 2.32 (s, 3H), 2.24-1.19 (m, 12H); MS (*m\z*); 308 (M^+, 59.17%).

1-(4-(Substitutedalkenyl)phenyl)-4-(1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazono)ethyl)-5-methyl-1*H*-pyrazole (9-13). ***General procedure***: Pyrazole derivatives **4-8.** (0.63 mmol) were dissolved in absolute ethanol (10 mL), and then 2-hydrazinyl-4,5-dihydro-1*H*-imidazole hydrobromide (11.5 mg, 0.63 mmol), and hydrochloric acid (0.1 mL) were added. The reaction mixture was heated at reflux for 16-hours. The solvent was concentrated under reduced pressure, poured onto crushed ice, and neutralized with sodium carbonate (to pH 7-8). The solid precipitate was collected by filtration and washed with copious amount of water. Crystallization from absolute methanol afforded the desired products as solids. Yields, physical properties, and spectral data of isolated purified products are listed below:

1-(4-(cyclopentylidenemethyl)phenyl)-4-(1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazineylidene) ethyl)-5-methyl-1*H*-pyrazole (9). Yellow solid (62 mg, 52%); ^{1}H NMR (DMSO-d_6) δ: 11.32 (brs, 1H), 8.03 (s, 1H), 7.62 (brs, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.44 (s, 1H), 3.75 (s, 4H), 2.45 (s, 3H), 2.33 (s, 3H), 1.82-1.62 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 156.4, 149.2, 143.6, 140.3, 138.2, 137.3, 129.8, 128.6, 125.6, 119.6, 48.2, 34.8, 23.4, 17.1, 13.3; HRMS (EI) *m/z* 362.2221 M^+, calc. for Anal. $C_{21}H_{26}N_6$ 362.2219 M^+.

1-(4-((*E*)-2-cyclohexylvinyl)phenyl)-4-((*E*)-1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazineylidene) ethyl)-5-methyl-1*H*-pyrazole (10). yellow solid (77 mg,65%); ^{1}H NMR (DMSO-d_6) δ: 11.32 (brs, 1H), 7.88 (s, 1H), 7.62 (brs, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.37 (dd, *J* = 16.0, 6.8 Hz, 1H), 3.72 (s, 4H), 2.47 (s, 3H), 2.23 (s, 3H), 1.76-1.18 (m, 11H); ^{13}C NMR (DMSO-d_6) δ: 156.6, 149.4, 146.5, 137.7, 136.9, 130.9, 130.0, 127.8, 125.6, 120.2, 49.2, 43.5,

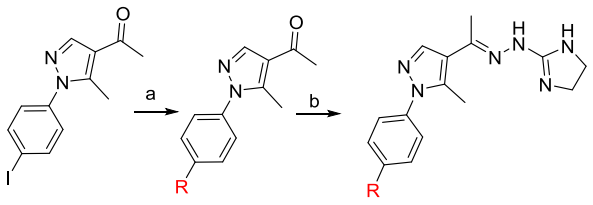
32.8, 25.9, 16.3, 13.4; HRMS (EI) *m/z* 390.2532 M^+, calc. for Anal. $C_{23}H_{30}N_6$ 390.2536 M^+.

1-(4-((*E*)-3-cyclopentylprop-1-en-1-yl)phenyl)-4-((*E*)-1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydra- zineylidene)ethyl)-5-methyl-1*H*-pyrazole (11). yellow solid (69 mg, 58%); ^{1}H NMR (DMSO-d_6) δ: 11.15 (brs, 1H), 8.01 (s, 1H), 7.62 (brs, 1H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 6.50 (d, *J* = 16.1 Hz, 1H), 6.41 (dd, *J* = 16.1, 6.4 Hz, 1H), 3.62 (s, 4H), 3.05 (tt, *J* = 16.1, 8.6 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H), 2.09-2.05 (m, 1H), 1.91-1.61 (m, 8H); ^{13}C NMR (DMSO-d_6) δ: 168.1, 156.4, 149.5, 146.7, 137.6, 136.8, 131.1, 130.1, 127.9, 125.8, 120.3, 47.2, 43.5, 38.3, 32.8, 25.4, 16.6, 13.3; HRMS (EI) *m/z* 390.2532 M^+, calc. for Anal. $C_{23}H_{30}N_6$ 390.2536 M^+.

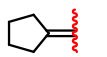
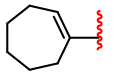
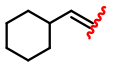
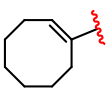
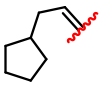
1-(4-(cyclohept-1-en-1-yl)phenyl)-4-(1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazineylidene)ethyl)-5-methyl-1*H*-pyrazole (12). white solid (63 mg, 53%); ^{1}H NMR (DMSO-d_6) δ: 11.06 (brs, 1H), 8.04 (s, 1H), 7.55 (brs, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 1H), 3.66 (s, 4H), 2.46 (s, 3H), 2.33 (s, 3H), 2.00-1.22 (m, 10H); ^{13}C NMR (DMSO-d_6) δ: 156.3, 149.4, 147.7, 140.4, 138.3, 137.1, 129.8, 125.4, 123.2, 119.1, 45.3, 29.4, 28.1, 25.2, 17.1, 13.3; HRMS (EI) *m/z* 376.2375 M^+, calc. for Anal. $C_{22}H_{28}N_6$ 376.2378 M^+.

1-(4-((*E*)-cyclooct-1-en-1-yl)phenyl)-4-((*E*)-1-(2-(4,5-dihydro-1*H*-imidazol-2-yl)hydrazineylidene) ethyl)-5-methyl-1*H*-pyrazole (13). white solid (79 mg, 66%); ^{1}H NMR (DMSO-d_6) δ: 11.06 (brs, 1H), 8.03 (s, 1H), 7.76 (brs, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.46 (s, 1H), 3.47 (s, 4H), 2.47 (s, 3H), 2.32 (s, 3H), 2.22-1.17 (m, 12H); ^{13}C NMR (DMSO-d_6) δ: 156.6, 148.9, 147.5, 140.4, 138.1, 137.7, 132.2, 129.4, 126.9, 125.9, 119.5, 48.2, 33.6, 33.1, 32.2, 25.1, 17.1, 13.4; HRMS (EI) *m/z* 390.2532 M^+, calc. for Anal. $C_{23}H_{30}N_6$ 390.2536 M^+.

Scheme 1



3 4-8 9-13

Comp.	R	Comp.	R
4, 9		7, 12	
5, 10		8, 13	
6, 11			

Reagent and coditions: (a) Proper terminal alkenes, pd$(AcO_2)_2$, K_2CO_3, DMF, heat at 80 ^{0}C 24 h, (b) Hydrazino imidazoline HBr, EtOH, Conc. HCl heat to12 h.

Antimicrobial Activity

Antimicrobial investigation:

The minimum inhibitory concentrations (MICs) of the tested compounds and control drugs; linezolid, vancomycin, gentamicin (antibiotics), azithromycin and 5-fluorocytosine (5-FC) (antifungal drug) were determined using the broth microdilution method, according to guidelines outlined by the Clinical and Laboratory Standards Institute CLSI) (Clinical and Laboratory Standards Institute 2007, Clinical and Laboratory Standards Institute 2008, Clinical and Laboratory Standards Institute 2012) or as described in previous reports (Geers and Donabedian 1989), with some modifications, against clinically-relevant bacterial (methicillin-resistant Staphylococcus aureus (MRSA), Escherichia coli, Clostridium difficile and Neisseria gonorrhea strains) and fungal (Candida albicans) strains. S. aureus and E. coli were grown aerobically overnight on tryptone soy agar plates at 37° C. C. difficile was grown anaerobically on brain heart infusion supplemented agar at 37° C for 48 hours. *N. gonorrhoea* was grown on Brucella broth supplemented with yeast extract, neopeptone, hematin, pyridoxal and NAD at 37° C for 24 hours in presence of 5% CO_2. *C. albicans* was grown aerobically overnight on yeast peptone dextrose (YPD) agar plate at 35° C. Afterwards, a bacterial solution equivalent to 0.5 McFarland standard was prepared and diluted in cation-adjusted Mueller-Hinton broth (CAMHB) (for S. aureus and E. coli) to achieve a bacterial concentration of about 5 × 105 CFU/mL. C. difficile was diluted in brain heart infusion supplemented broth, supplemented with yeast extract, hemin and vitamin K to achieve a bacterial concentration of about 5 × 105 CFU/mL. N. gonorrhoeae was diluted in Brucella broth supplemented with yeast extract, neopeptone, hematin, pyridoxal and NAD to achieve a bacterial concentration of about 1 × 106 CFU/mL. C. albicans was diluted in Roswell Park Memorial Institute (RPMI 1640) medium with glutamine and without bicarbonate (GIBCO by Life Technologies, Green Island, NY, USA) which was buffered to pH 7.0 with 0.165 M of [3-(N-morpholino) propanesulfonic acid] (MOPS) (dot scientific inc., Burton, MI, USA) to achieve a fungal concentration of about 1.5 × 103 CFU/mL. Compounds and control drugs were added in the first row of the 96-well plates and serially diluted with the corresponding media containing bacteria/fungi. Plates were then, incubated as previously described. MICs reported in Table (1) are the minimum concentration of the compounds and control drugs that could completely inhibit the visual growth of bacteria/fungi.

Code	Methicillin-resistant *S. aureus* NRS384 (MRSA USA300)	*Clostridium difficile* ATCC BAA 1870	*Escherichia coli* JW55031 (TolC Mutant)	*Escherichia coli* BW25113 (wild-type strain)	*Neisseria gonorrhoeae* 181	*Candida albicans* SS5314 (wild-type)
٤	>64	64	>64	>64	>64	64
٥	>64	>64	>64	>64	>64	>64
٦	>64	>64	>64	>64	>64	>64
٧	>64	>64	>64	>64	>64	>64
٨	>64	>64	>64	>64	>64	>64
9	**16**	**32**	**16**	**64**	**64**	**16**
10	**8**	**16**	**8**	**32**	**0.25**	**8**
11	**32**	**16**	**16**	**32**	**16**	**16**
12	**16**	**4**	**8**	**32**	**16**	**16**
13	**32**	**64**	**32**	**128**	**32**	**16**
Linezolid	**1**	**1**	**8**	**>128**	**NT**	**NT**
Vancomycin	**1**	**1**	**NT**	**NT**	**NT**	**NT**
Gentamicin	**NT**	**NT**	**0.25**	**0.5**	**NT**	**NT**
5-Fluorocytosine	**NT**	**NT**	**NT**	**NT**	**NT**	**0.25**
Ceftiaxone	**NT**	**NT**	**NT**	**NT**	**0.015**	**NT**

Table (1); Antimicrobial activities of compounds **4-13**.

Conclusion

From the above mentioned results in table (1) it was found that (for the On MRSA-US300 activity) the highest activity obtained with compound **10** with MIC value about 8 µg/mL followed by compound **12** with MIC value about 16 µg/mL. The other compounds show very low activity. On the other hand, most synthesized compounds gave very weak activity against *Clostridium difficile* ATCC BAA 1870 except compound **12** which has moderate activity with MIC 4 µg/mL. Compound **12** have weak activity but still active against *C. difficile*. This means that the presence of terminal hydrogen bond acceptor group is essential for activity against resistant gram positive bacteria. For the activity against gram negative tested *Escherichia coli* JW55031 (TolC Mutant) all newly synthesized compounds show no activity except compounds **10** and **14** which showed weak activity with MIAC 8 µg/Ml.

As a conclusion phenylpyrazole is a promising scaffold that may be useful for the development of new antimicrobials to overcome antimicrobial resistant strains specially gram-positive ones and fungi.

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تشييد و تقييم الفاعلية الميكروبية لمشتقات الفينيل بيرازول

على حسن على حماد ، عبد الرحمن صلاح ميهوب ، محمد السيد يوسف السواح ، أشرف حسن بيومى

قسم الكيمياء العضوية – كلية الصيدلة (بنين) – جامعة الأزهر- القاهرة- مصر

- تعد ظاهرة النمو السريع لمقاومة المضادات الحيوية أمراً مقلقاً لكل العاملين والمهتمين بمجال الصحة العامة والصيدلة الاكلينيكية. فعلي الرغم من وجود ترسانة قوية من المضادات الحيوية فإن الكثير من تلك المركبات ذات القيمة العالية قد وقع بالفعل ضحية للتوسع الرهيب والمفاجئ في المقاومة من قبل العديد من البكتيريا المسببة للأمراض. ومن هذا، فإنه طبقاً لتقرير مركز السيطرة على الأمراض والوقاية منها فإن ظاهرة البكتيريا المقاومة للمضادات الحيوية قد أدت إلى تسجيل ٢٣٠٠٠ حالة وفاة في الولايات المتحدة الأمريكية وحدها في عام ٢٠١٥.
- هذا وقد ثبت النشاط الواعد الذي يضطلع به مركبات الفينل بيرازول ضد مسببات الأمراض البكتيرية المقاومة للأدوية المتعددة، ولا سيما المكورات العنقودية الذهبية المقاومة للميثيسيلين، بسبب تأثيرها المباشر على مستهدف جديد داخل جدار الخلايا. وتمت دراسة العلاقة بين تركيبها الكيميائى وفاعليتها ضد هذا المستهدف من خلال تحضير ما يزيد على ٤٠٠ مركب من مشتقاتها وتقييم تأثيرها البيولوجى ودراسة الحركية الدوائية لبعضها.
- هنا، قمنا بتصميم وتخليق ودراسة التاثير البيولوجى لسلسلة من مركبات الفينيل بيرازول التى سجلت اقوى فاعلية وافضل خصائص من حيث الذوبانية وطول عمر النصف وفقا لدراسة العلاقة بين التكوين الكيميائى والفاعلية ، وذلك بهدف الحصول على سلسلة جديدة من المركبات التى تؤثر على هذا النوع من البكتيريا . وقد أعاقت المركبات الواعدة نمو السلالات السريرية ذات الصلة للمكورات العنقودية الذهبية المقاومة للميثيسيلين في المختبر عند تركيزات منخفضة تصل إلى ٨ ملغم/ مل، ومارست تأثيرها المضاد للبكتيريا بمنع في تخليق جدار الخلية البكتيرية عن طريق تثبيط الإنزيم المكون للأندكابرينيل ثنائي الفوسفات وأندكابرينيل ثنائي الفوسفات الفوسفاتيز.
- أدت الدراسة الى إكتشاف مركبان من مركبات الفينيل بيرازول (المركبات١٠,١٢) التي نجحت في القضاء على المكورات العنقودية الذهبية المقاومة للميثيسيلين داخل البلاعم (Macrophages) المصابة.