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COMMUNICATION

Pyrazole-Thiazole Core-Containing Analogs Exhibit Adjunctive Activity with Meropenem against Carbapenem-Resistant *Enterobacteriaceae* (CRE)

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Abstract: Pyrazole-thiazole core-containing compound KP-40 and 20 novel derivatives were designed and synthesized through traditional SAR analysis. These molecules displayed adjunctive activity with meropenem against Gram-negative bacteria evidenced by a range of fractional inhibitory concentration (FIC = 0.5 – 0.25) and minimum adjunctive concentration (MAC = 128 – 32 μM) values. Of this series of molecules, four compounds displayed notable adjunctive potential, with FIC and MAC values of 0.25 and 32 μM, respectively. Moreover, the solubility of these compounds was improved to an acceptable range. Further analysis using our "in house" permeation and efflux multi parameter optimization (PEMPO) algorithm revealed key physicochemical properties that may be critical for the development of active Gram-negative antibacterials. Taking PEMPO scores into consideration prior to executing synthesis of analogs may be a simple, yet rapid and effective strategy that can be used in conjunction with traditional SAR approaches to aid in the design of potent Gram-negative antibacterials.

Multidrug-resistant (MDR) bacterial infections are an emerging global public health concern that has escalated at an alarming rate over the last decade.[1] These emerging pathogens are a grave threat in healthcare settings and are responsible for a variety of infections such as urinary tract infections, bloodstream infections, and pneumonia.[2] Carbapenem antimicrobials are a last-line defense against MDR pathogens and, until recently, have demonstrated to be reliable broad-spectrum treatments for numerous bacterial infections.[3] Carbapenem-resistant *Enterobacteriaceae* (CRE) encompass a group of MDR bacteria that has emerged over the last few decades.[4] CREs exhibit resistance to all currently available β-lactam antibiotics including, by definition, carbapenems and are often resistant to aminoglycosides, fluoroquinolones, and tetracyclines.[4] In the United States alone, CREs were estimated to cause 13,000 infections in hospitalized patients and 1,100 deaths in 2017.[5] A major challenge in developing efficacious antibiotics against certain MDR pathogens is overcoming particular enzymatic and structural features that undermine antibiotic activity in Gram-negative bacteria. Unlike their Gram-positive counterparts, Gram-negative bacteria contain an outer lipopolysaccharide membrane which impedes the entrance of many otherwise active antimicrobials into the bacterial cell. This added barrier, coupled with ubiquitous expression of efflux pumps, prevents most antibiotics from reaching their biomolecular target and exhibiting their antibacterial activity.

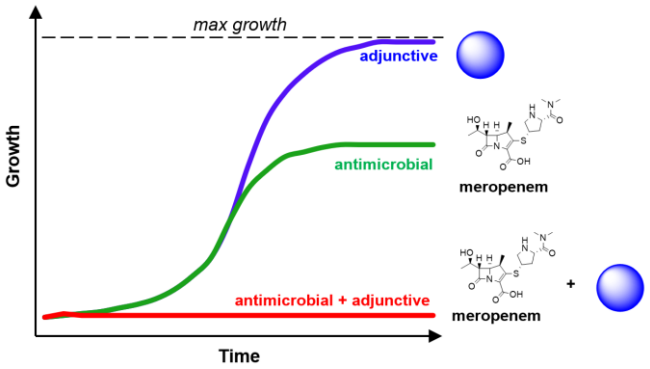


Figure 1. Representative growth curves of MDR pathogens in the presence of an adjunctive (blue), an antimicrobial (green), or a combination of antimicrobial and adjunctive (red). The combinatorial administration of the two compounds is more effective than the administration of either compound on its own.

Carbapenems overcome both of these challenges and retain detectable *in vitro* [6] and *in vivo* [7] activity in Gram-negative bacteria. In CREs, however, with the expression of lactam hydrolyzing carbapenemases, resistance to this class of β-lactam antibiotics emerged.[8] Carbapenemases pose a new challenge that warrants new strategies for addressing these resistant pathogens. Developing new drug candidates with unique mechanisms of action is a time-intensive endeavor which may involve understanding the target and development of robust assays for validating biological activity. Alternatively, it may be more attractive to identify small molecules that block mechanisms of resistance and thereby potentiate and restore clinically meaningful activity of existing antibiotics (Figure 1). A synergistic combination of small molecule potentiators and carbapenems, for example, may restore antibacterial activity of carbapenems against otherwise resistant CREs. This approach would enable the continued use of these efficacious antibiotics which have an excellent safety record. Recently the Martin group reported a synergistic effect between two thiol-containing small molecules, serving as metallo-β-lactamase (MBL) inhibitors, and the broad-spectrum antibiotic, meropenem.[9] The ability of the two MBL inhibitors to potentiate the activity of meropenem correlated with their zinc-binding ability, with measured K_d values of 9.8 and 20.0 μM. The several FDA-approved diazabicyclooctane, serine β-lactamase inhibitors are also examples of use of direct adjunctive inhibitors of prevalent carbapenemases to restore carbapenem activity.[10] We also recently considered the identification of anti-plasmid agents as adjunctives to eliminate plasmid-borne antibiotic resistance elements and thereby restore antibiotic susceptibility.[11] With the goal of identifying additional compounds with adjunctive potential, agnostic of mechanism of action, our

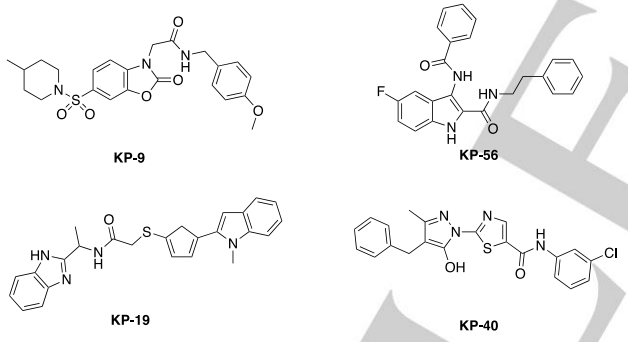
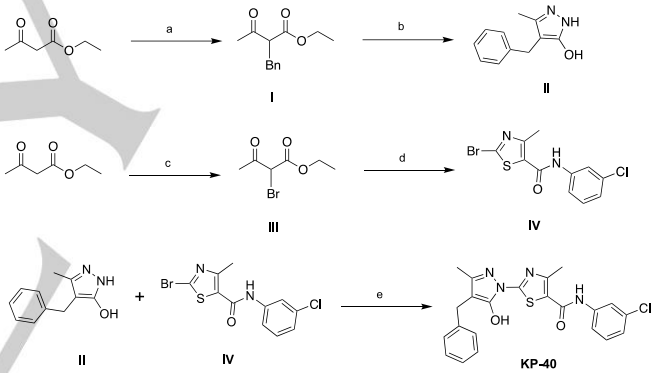


Figure 2. Compounds selected for resynthesis from screening and cheminformatics filtering results. A library of 182,427 commercially available compounds were screened for adjunctive activity with meropenem against representative carbapenem-resistant *Enterobacteriaceae* (CRE) strains. After a series of confirmatory screens, the narrowed hit list underwent a layer cheminformatics processing – leading to the removal of pan-assay interference compounds (PAINS) and construction of structural similarity clusters. KP-9, KP-56, KP-19, and KP-40 were selected for resynthesis based on their potency, spectrum of activity and predicted physicochemical properties.

previous work employed our validated screening/counter-screening method[12] to probe the ability of a large collection of small molecules to potentiate meropenem against a *Klebsiella pneumoniae* CRE strain[13]. As previously described, we screened a 182,427 compound library with and without previously characterized biological activity in duplicate using this two-tiered assay. We initially identified 604 (0.332 %), 599 (0.328 %) and 43 (0.02 %) weak, medium, and strong adjunctive hits, respectively. After applying a primary filter which removed compounds exhibiting <50% inhibition and a secondary filter removing compounds with eukaryotic cell cytotoxicity, 658 adjunctive hits were obtained. Of these hits, 274 compounds were selected based on primary screening potency for confirmatory analysis using cherry picks from commercial library plates in a manner identical to the primary screening assay. A 25% inhibition cut off was used for this secondary analysis which yielded 127 adjunctive hits. A cheminformatics filtering process was then applied, removing nonspecific pan-assay interference compounds (PAINS), leading to the removal of 20 hits. The remaining 107 adjunctive hits were clustered using two-dimensional fingerprint-based structural similarity, generating 15 clusters and 17 singletons. Finally, compounds within each cluster were ranked using a previously reported multi-parameter optimization (MPO) algorithm.[14] Originally developed for CNS drugs, MPO scores take six physicochemical properties into account in order to predict the potential of drug molecules to permeate the blood-brain barrier. Higher MPO scores have also shown to correlate with more desirable physicochemical attributes, leading to greater bioavailability. Furthermore, an "in-house" MPO algorithm, termed permeation and efflux MPO (PEMPO), was designed to predict the ability of a compound to permeate the outer lipopolysaccharide membrane of Gram-negative bacteria and avoid efflux – two essential characteristics of effective Gram-negative antimicrobial compounds.[13] 42 compounds, representing 15 clusters, and 6 singletons were identified for

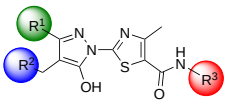


Scheme 1. Synthetic route for the preparation of KP-40: a) ^{t}BuOK, THF, 0 ºC, 30 min., BnBr, reflux, 12 h; b) N_2H_4, EtOH, reflux; c) NBS, *p*-TsOH, DCM, 0 ºC to r.t. 2 h; d) i. NaOH (2.5 M), ethanol, reflux; ii. $SOCl_2$, *m*-chloroaniline, DCM, pyridine, reflux; iii. thiourea, ethanol, reflux; iv. $CuBr_2$, ^{t}BuONO, CH_3CN; e) microwave, CuBr, Cs_2CO_3, DMF.

secondary analysis through this process. In order to ascertain the degree to which compounds exhibit a synergistic effect with meropenem, fractional inhibitory concentration (FIC) values,[15] defined as the minimum inhibitory concentration (MIC) of meropenem in the presence of the adjunctive compound over the MIC of meropenem alone, were measured. Select compounds were then identified for resynthesis and confirmatory testing based on FICs, potency, and desirable physicochemical properties. For adjunctive antimicrobials, the minimum adjunctive concentration (MAC, i.e., minimal concentration needed to reduce the MIC of meropenem 4-fold) were determined. Of these resynthesized compounds, 2-(4-benzyl-5-hydroxy-3-methyl-1*H*-pyrazol-1-yl)-*N*-(3-chlorophenyl)-4-methylthiazole-5-carboxamid KP-40 (Figure 2) was selected as a favored adjunctive partner of meropenem for follow-up structure-activity relationship (SAR) studies based on consistent FIC values observed between the library sample (FIC = 0.31) and the "in-house" synthesized sample (FIC = 0.42). By designing structural diversity in KP-40 derivatives, we aim to reduce FIC and MAC values, thus

improving the synergistic potential of the compounds identified in our original work. The chemical structure of KP-40 consists of a hybrid heterocyclic pyrazole-thiazole core. Individually, these heterocyclic moieties have previously been reported for their antimicrobial activity against Gram-positive and Gram-negative pathogens.[16] In addition, the synthesis of KP-40 has some advantages in terms of facile synthesis and easily accessible functional group modifications. To prepare the pyrazole (**II**) fragment, *α*-benzylation of ethyl acetoacetate was performed by condensation. The benzylated intermediate (**I**)[17] with hydrazine hydrate afforded heterocyclic hydroxyl-pyrazole fragment (**II**) via a condensation-intramolecular cyclization-aromatization cascade reaction.[18] The synthesis of thiazole fragment (**IV**) commenced with construction of the *α*-bromo ethyl acetoacetate intermediate (**III**) [19] using NBS as a bromine source in a polar solvent, which readily reacts with thiourea under reflux conditions to afford heterocyclic 2-aminethiazole in a high yield.[20] This was followed by the Sandmeyer reaction via a diazonium salt intermediate, 2-aminethiazole, using $CuBr_2$ which successfully yielded the target heterocyclic 2-bromothiazole framework.[20] The ester group of 2-bromothiazole was hydrolyzed at the C5 position under basic conditions using NaOH (2.5 M) in good yield. Finally, 2-bromothiazole acid was transformed into 2-bromothiazole (**IV**) via acylation using thionyl chloride. With the two main heterocyclic fragments in hand, a final coupling reaction was carried out between hydroxy-pyrazole (**II**) and 2-bromothiazole (**IV**) under microwave irradiation using Cu(I) as the coupling catalyst.[21] The convergent synthesis of KP-40 was successfully completed in 8 total steps (Scheme 1).

Table 1. MAC and FIC values of KP-40 derivatives from initial SAR study.

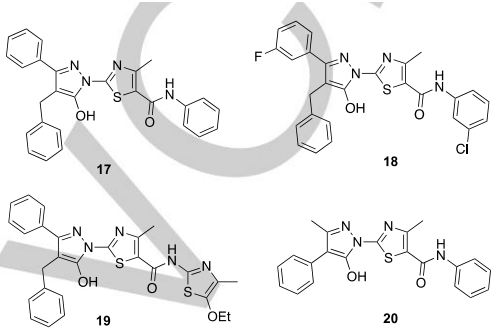


no	R^1	R^2	R^3	FIC [a]	MAC [b]
1	Me	Ph	Ph	0.5	64
2	Me	Ph	Ph-4OPh	0.25	64
3	Me	Ph	Ph-4Ph	0.25	64
4	Me	3-OMe-6-nitroPh	m-ClPh	0.25	64
5	Me	3-OMe-6-nitroPh	Ph	0.25	64
6	Me	m-CF_3Ph	Ph	0.25	64
7	Me	3,5-diOMePh	Ph	0.25	64
8	^{t}Bu	Ph	m-ClPh	0.25	64
9	Ph	m-CF_3Ph	Ph	0.5	64
10	Ph	3,5-diOMePh	Ph	0.25	128
11	Ph	Ph	Ph-4OPh	0.25	128
12	Ph	Ph	Ph-4Ph	0.25	128
13	Ph	Ph	4,5-diMethiazole	0.25	128
14	p-OMePh	Ph	m-ClPh	0.25	128
15	p-OMePh	Ph	Ph	0.25	64
16	p-CF_3Ph	Ph	Ph	0.25	64

[a] Calculated from quadruplicate testing against *Klebsiella pneumoniae* BIDMC12A. [b] MAC unit is μM.

Our initial SAR investigation began with retention of the methyl group on the R^1 position and modification of the R^2 and R^3 groups in order to determine potential functional group dependence and activity at these sites. First, an unfunctionalized phenyl group was introduced at R^3 (entry **1**), allowing us to examine the influence of the chloro substituent in KP-40. FIC and MAC values of 0.50 and 64 μM, respectively were observed indicating that chlorine substitution may not be essential for synergistic activity. The introduction of more flexible and longer aryl groups at the R^3 position (entry **2** and **3**) delightfully led to a 2-fold decrease in the FIC value. Next, we examined the R^2 position with a mix of electron-withdrawing and electron-donating groups (entry **4**) and the analog exhibited a 0.25 FIC value and 64 μM MAC. The removal of the *meta*-chloro substituent at the R^3 position (entry **5**) led to retention of FIC and MAC values when compared to analog **4**. Afterwards, analogs with electron-withdrawing (entry **6**) and electron-donating (entry **7**) moieties were prepared in order to examine the influence of electron density at the R^3 position. However, both designs displayed the same results despite the difference in electron density. Following the investigation of R^2 and R^3 modifications, we altered the functionality at R^1 by first introducing a bulky *tert*-butyl group (entry **8**). Adjunctive antimicrobial activities of this analog resembled that of KP-40. We further examined the effects of R^1 substitution by incorporating a less bulky, aromatic group. Simultaneous incorporation of a CF_3 group at R^2 (entry **9**) was conducted based on the well-known advantageous steric and electronic properties that this bioisostere exhibits. Unfortunately, analog **9** exhibited a worse FIC value (0.5) than the previous few entries. Interestingly, the presence of the electron-donating group, 3,5-dimethoxyphenyl (entry **10**), showed a reverse result indicated by an increased FIC but a 2-fold decrease in MAC (128 μM) compared to compound **10**. Entries **11** and **12** have longer aromatic substituents at the R^3 position and both display 128 μM MAC values. Even heterocycle-containing compound **13** showed the same activity as entries **11** and **12**. Compounds **14** and **15** were prepared in order to examine

Table 2. Activity and solubility data of the most potent KP-40 derivatives.



no	FIC	MAC[a]	cLog $D_{7.4}$	cLog P	Sol.
17	0.25	32	5.22	6.67	< 1
18	0.25	32	5.96	7.42	< 1
19	0.25	32	5.06	6.51	27.6 uM
20	0.25	32	2.84	4.32	26.9 uM

[a] MAC unit is μM.

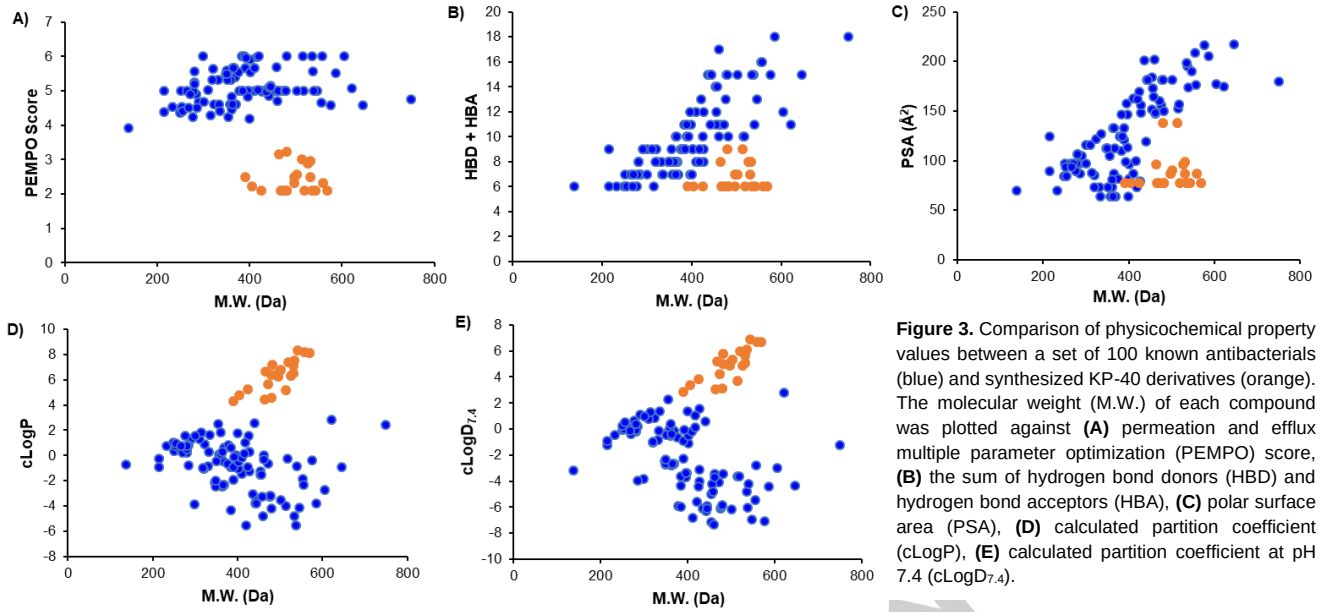


Figure 3. Comparison of physicochemical property values between a set of 100 known antibacterials (blue) and synthesized KP-40 derivatives (orange). The molecular weight (M.W.) of each compound was plotted against **(A)** permeation and efflux multiple parameter optimization (PEMPO) score, **(B)** the sum of hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA), **(C)** polar surface area (PSA), **(D)** calculated partition coefficient (cLogP), **(E)** calculated partition coefficient at pH 7.4 ($cLogD_{7.4}$).

the adjunctive activity change when the electron density of the R^1 group is modulated. The electron-donating group, *p*-methoxyphenyl, was added in entry **14** and displayed the same FIC but a higher MAC value. The MAC value improved 2-fold when the chlorine substituent in the aromatic R^3 group was removed. Our attempts to increase activity by adding a CF_3 group at the R^1 position was unsuccessful, demonstrated by similar FIC and MAC values as the previous analogs. After our initial SAR studies, we identified several patterns that would guide our following synthetic pursuits - 1) R^1 group does not play a critical role in providing a synergistic effect 2) electron-withdrawing groups decrease FIC values 3) elongated aromatic groups have no influence on the activity and solubility. Based on our synthetic strategy, we designed and prepared diverse analogs with some compounds displaying 2- to 4-fold improvements in MACs while retaining FIC values. Entries **17** and **18** consist of aromatic rings at R^1, R^2, and R^3 positions and, consequently, their solubility was hampered due to the high density of phenyl groups. To enhance the solubility, a heteroaromatic group was introduced (entry **19**) at the R^3 position and its solubility appropriately increased to 27.6 μM, while retaining its synergistic activity. Finally, removal of the methylene unit at R^2 generated analog **20** which, gratifyingly, retained the activity and solubility of entry **19**. While some improvements in FIC and MAC values were observed, the analogs generated during this SAR study did not exhibit satisfactory synergism in combination with meropenem. A potential reason for these disappointing results may be that the physicochemical attributes of our analogs are not appropriate for targeting Gram-negative bacteria. Previous examinations of approved antibacterial versus non-antibacterial libraries have highlighted a striking difference in physicochemical properties between the two.[22] More specifically, antibacterial compounds tend to be larger and more polar – demonstrated by higher M.W, HBD, HBA, PSA values and lower cLogP and $cLogD_{7.4}$ values when compared to non-antibacterials. Additionally, antibacterials typically possess one or more ionizable groups at pH 7.4 which presumably assists in the molecule's ability to permeate the bacterial membrane. Therefore, when designing antibacterial compounds, employment of traditional medicinal chemistry optimization strategies may not be suitable. We previously reported the use of our "in-house" MPO algorithm (PEMPO) to compare our screened hits with known antibacterials.[13] This score differs from the classical MPO algorithm in that it places priority on key physicochemical properties, and their optimal ranges, that are believed to be important for penetration and avoidance of efflux in Gram-negative bacteria. PEMPO scores range from 0 to 6, with 6 indicating optimal permeation and minimal efflux potential while 0 indicates a lack of such potential. In order to examine whether our synthesized analogs possess the properties essential for Gram-negative antibacterial activity, we calculated PEMPO scores for each of the compounds. We reported that the average PEMPO score for 100 known antibacterials was determined to be 5.08. In comparison, our synthesized analogs exhibit an average PEMPO score of 2.43, with entry **5** displaying the highest value of 3.22. Further inspection of the 6 physicochemical properties used to construct these scores revealed the reason for the drastic difference observed between the two data sets. To summarize, our compounds are too lipophilic, indicated by average HBD, HBA, PSA, $cLogD_{7.4}$, and cLogP values of 2.0, 4.7, 88 Å, 4.93, and 6.36, respectively. By contrast, the set of 100 known antibacterials exhibit average HBD, HBA, PSA, $cLogD_{7.4}$, and cLogP values of 2.9, 7.0, 127 Å, -2.28, and -0.86, respectively.[22] The divergence in values is visually represented in Figure 3 and underscores the vast disparity between compounds designed with "drug-likeness" in mind and those that are designed with emphasis on optimizing the properties critical to bacterial membrane penetrance and avoidance of efflux. Synthetic tractability is likely to contribute to this disparity, as compounds with a greater PSA and higher number of HBDs and HBAs are generally harder to synthesize. As a result, the chemical space of potential drug molecules is narrowed, thereby limiting the degree to which efficacious antibacterials are discovered. By utilizing PEMPO scores as a primary criterion for the selection of designed analogs, we might capture features most relevant to antibacterial activity and improved our results.

Overall, we conclude that KP-40 and its SAR-designed analogs were adjunctive partners with meropenem. We successfully synthesized 20 novel analogs of compound **1** with pyrazole-thiazole core moieties. Within this new series of compounds,

several showed potent activity across a range of FIC and MAC values. However, satisfactory synergistic activity with meropenem was not observed among any of the analogs. Our previous report suggested that these findings may reflect the limited potential of our screening compound libraries due to significant enrichment for molecules with "drug-likeness" properties, which generally do not align with biologically active antibacterials. Results presented here and our prior analysis suggests that PEMPO scores may provide a pivotal guideline for antimicrobial screening library optimization and rational design for future screening efforts based on consideration of physicochemical properties deemed to be important for penetration of the outer membrane and avoidance of efflux mechanisms.

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Keywords: antibacterial activity • Carbapenem-Resistant Enterobacteriaceae • adjunctive activity • meropenem

[1] a) Y. Briers, M. Walmagh, V. V. Puyenbroeck, A. Cornelissen, W. Cenens, A. Aertsen, H. Oliveira, J. Azeredo, G. Verween, J. Prinay, S. Miller, G. Volckaert, R. Lavignea, m*Bio,* **2014**, *59*, e01379-14. b) M. H. Kollef, Y. Golan, S. T. Micek, A. F. Shorr, M. I. Restrepo, *Clin. Infect. Dis.* **2011,** *53*, 33-55**.** c) C. Yilmaz, G. Ozcengiz, *Biochemical Pharmacology*, **2017**, *133*, 43-62. d) A. K. Konreddy, G. U. Rani, K. Lee, Y. Choi, *Cur. Med. Chem*. **2019**, *26*, 5363-5388.

[2] a) R. K. Flamm, D. J. Farrell, H. S. Sader, R. N. Jones, *J. Antimicrob. Chemother.* **2014**, *69*, 1589-1598. b) D. M. Sievert, P. Ricks, J. R. Edwards, A. Schneider, J. Patel, A. Srinivasan, A. Kallen, B. Limbago, S. Fridkin, *Infect. Control Hosp. Epidemiol*, **2013**, *34*, 1-14. c) R. Gaynes, J. R. Edwards, *Clin. Infect. Dis.* **2005,** *41*, 848-854**.** d) K. J. Popovich, B. Hota, R. Hayes, R. A. Weinstein, M. K. Hayden, *Infect. Control Hosp. Epidemiol,* **2009**, *30*, 959-963.

[3] a) G. G. Zhanel, R. Wiebe, L. Dilay, K. Thomson, E. Rubinstein, D. J. Hoban, A. M. Noreddin, J. A. Karlowsky, *Drug.* **2007**, *67*, 1027-1052. b) R. D. Pryka, G. M. Haig, *Ann. Pharmacother,* **1994**, *28*, 1045-1054. c) J. J. Schafer, D. A. Goff, J. E. Mangino, *Clin. Infect. Dis.* **2009,** *4*, 18-28**.**

[4] a) N. Gupta, B. M. Limbago, J. B. Patel, A. J. Kallen, *Clin. Infect. Dis.* **2011,** *53*, 60-67**.** b) L. K. Logan, R. A. Weinstein, *J. Infect. Dis,* **2017**, *215*, 28-36. c) D. V. Duin, K. S. Kaye, E. A. Neuner, R. A. Bonomo, *Diagn. Micr. Infec. Dis.* **2013,** *75*, 115-1204**.** d) H. J. Morrill, J. M. Pogue, K. S. Kaye, K. L. LaPlante, *Open Forum Infect. Dis.* **2015,** *2*, 1-15**.** e) R. F. Potter, A. W. D'Souzaa, G. Dantas, *Drug. Resist. Updat.* **2016,** *29*, 30-46**.** f) H. M. Zowawi, B. M. Forde, M. Alfaresi, B. Alzarouni, Y. Farahat, T. Chong, W. Yin, K. Chan, J. Li, M. A., Schembri, S. A. Beatson, D. L. Paterson, *Sci. Rep.* **2015,** *5.* 15082-15090**.**

[5] L. M. Weiner, A. K. Webb, B. Limbago, *Infect. Control. Hosp. Epidemiol.* **2016**, *37*, 1288–1301.

[6] Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019 Report.

[7] R. Fattouh, N. Tijet, A. McGeer, *Antimicrob. Agent Chemother.* **2015**, *60,* 1556-1559.

[8] D. M. Taylor, J. Anglin, S. Park, M. N. Ucisik, J. C. Faver, N. Simmons, Z. Jin, M. Palaniappan, P. Nyshadham, F. Li, J. Cambell, L. Hu, B. Sankaran, B. V. V. Prasad, H. Huang, M. M. Matzuk, T. Palzkill, *ACS. Infect. Dis.* **2020**, ahead of print. b) G. L. Daikos, S. Tsaousi, L. S. Tzouvelekis, *Antimicrob. Agents Chemother.* **2014**, *58*, 2322–2328.

[9] K. H. M. E. Tehrani, N. I. Martin, *ACS Infect. Dis.* **2017**, *3*, 711-717.

[10] T. B. Krohn, R. Manetsch, G. A. O'Doherty, J. E. Kirby, *Transl. Res.* **2020**, *220*, 14-32.

[11] K.E. Zulauf, J.E. Kirby, *Proc Natl Acad Sci USA*, **2020**, 117(47), 29839 – 29850.

[12] K. P. Smith, J. E. Kirby, *Assay Drug Dev. Technol.* **2016**, *14*, 194–206.

[13] K. P. Smith, M. Dowgiallo, L. Chiaraviglio, P. Prakash, C. Kim, R. Manetsch, J. E. Kirby, *SLAS Discovery*. **2019**, *24*(8), 842-853.

[14] T. Wager, X. Hou, P. R. Verhoest, A. Villalobos, *ACS Chemical Neuroscience*. **2010**, *1(6)*, 435–449.

[15] a) R. L. White, D. S. Burgess, M. Manduru, J. A. Bosso, *Antimicrob. Agents Chemother.* **1996***, 40,* 1914-1918. b) A. Serri, A. Mahboubi, A. Zarghi, H. R. Moghimi, *J. Pharm. Pharm. Sci.* **2019***, 22,* 10-21. c) P. Goni, P. Lopez, C. Sanchez, R. Gomez-Lus, R. Becerril, C. Nerin, *Food Chem.* **2009***, 116,* 982-989.

[16] a) O. Ebenezer, A. Singh-Pillay, N. A. Koorbanally, P. Singh, *Mol. Divers.* **2020***, 25,* in print. b) R. Gondru, K. Sirisha, S. Raj, S. K. Gunda, C. G. Kumar, M. Pasupuleti, R. Bavantula, *ChemistrySelect.* **2018***, 3,* 8270-8276. c) B. F. Abdel-Wahab, A. Sediek, H. A. Mohamed, G. E. A. Awad, *Eur. Lett. Drug. Des. Discov.* **2013***, 10,* 111-118. d) S. Bondock, W. Khalifa, A. A. Fadda, *Eur. J. Med. Chem.* **2007***, 42,* 948-954. e) K. Cheng, J. Xue, H. Zhu, *Bioorg. Med. Chem. Lett.* **2013***, 23,* 4235-4238. f) P. K. Sharma, N. Chandak, P. Kumar, C. Sharma, K. R. Aneja, *Eur. J. Med. Chem.* **2011***, 46,* 1425-1432. g) L. L. Xu, C. J. Zheng, L. P. Sun, J. Miao, H. R. Piao, *Eur. J. Med. Chem.* **2011***, 48,* 174-178. h) P. Khloya, P. Kumar, A. Mittal, N. K. Aggarwal, P. K. Sharma, *Eur. J. Med. Chem.* **2013***, 3,* 9-16.

[17] J. E. Beddow, S. G. Davies, K. B. Ling, P. M. Roberts, A. J. Russel, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem.,* **2007***, 5,* 2812-2825.

[18] a) L. A. Emert-Sedlak, H. M. Loughran, H. Shi, J. L. Kulp III, S. T. Shu, J. Zhao, B. W. Day, J. E. Wrobel, A. B. Reitz, T. E. Smithgall, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1480-1484. b) S. Nakao, M. Mabuchi, T. Shimizu, Y. Itoh, Y. Takeuchi, M. Ueda, H. Mizuno, N. Shigi, I. Ohshio, K. Jinguji, Y. Ueda, M. Yamamoto, T. Furukawa, S. Aoki, K. Tsujikawa, A. Tanaka, *Bioorg. Med. Chem. Lett,* **2014**, *24*, 1071-1074.

[19] a) M. Kirihara, S. Ogawa, T. Noguchi, K. Okubo, Y. Monma, I. Shimizu, R. Shimosaki, A. Htano, Y. Hirai, *Synlett*. **2006**, 14, 2287-2289. b) A. Srivastava, N. Jain, Tetrahedron **2013**, *69*, 5092-5097.

[20] R. Moldovan, R. Teodoro, Y. Gao, W. Deuther-Conrad, M. Kranz, Y. R. Wang, H. Kuwabara, M. Nakano, H. Valentine, S. Fischer, M. G. Pomper, D. F. Wong, R. F. Dannals, P. Brust, A. G. Horti, *J. Med. Chem.,* **2016***, 59,* 7840-7855.

[21] J. Suh, H. Kang, J. Kim, E. Yum, *Bull. Korean Chem. Soc,* **2012**, *33*, 2067-2070.

[22] R. O'Shea, H. E. Moser, *J. Med. Chem.* **2008**, *51*, 2871-2878.

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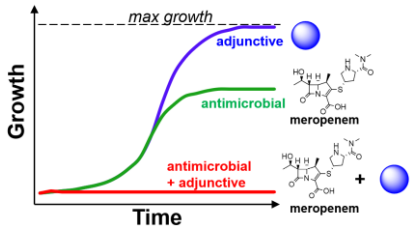

20 analogs of the antimicrobial adjunctive, **KP-40**, were synthesized. Analogs **17-20** displayed superior adjunctive activity (FIC =0.25, MAC = 32 µM) to **KP-40** when co-administered with meropenem. A comparison of physicochemical properties between our analogs and 100 known antibacterials revealed a notable distinction between the two sets. PEMPO scores may be used to better align properties of future analogs with that of known antibacterials.