Supplementary data

Halogenated Antimicrobial Agents to Combat Drug-Resistant Pathogens

Olajide Sunday Faleye[§], Bharath Reddy Boya[§], Jin-Hyung Lee, and Jintae Lee*

School of Chemical Engineering, Yeungnam University, 280 Daehak-Ro,

Gyeongsan, 38541, Republic of Korea (O.S.F., B.R.B., J-H.L., and J.L)

[§]These authors contributed equally to this work as first authors.

*Corresponding Author

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Address correspondence to

Jintae Lee, School of Chemical Engineering, Yeungnam University

280 Daehak-Ro, Gyeongsan, Gyeongbuk, 38541, Republic of Korea

E-mail: jtlee@ynu.ac.kr. Tel.: +82-53-810-2533. Fax: +82-53-810-4631

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Figure 1. Structures of halogenated polyphenols and essential oil compounds. **Catechol:** 6-chlorodopamine methacrylamide **(A)**, **magnolol**: 5,5'-dipropyl-3,3'-dibromo-2,2'-biphenyldiol **(B)**, (3,3'-dichloro5,5'-dipropyl-2,2'-biphenyldiol **(C)**, 5,5'-dibutyl-3,3'-diiodo-2,2'-biphenyldiol **(D)**, 5,5'-diallyl-3,3'-dibromo-[1,1'-biphenyl]-2,2'-diol **(E)**, SAR analysis of magnolol derivative **(F)**, **resveratrol:** 2-chloro-resveratrol **(G)**, 2-bromo-resveratrol **(H),** 4-[(*E*)-2-(4-chlorophenyl)ethenyl]phenol **(I)**, **flavonoids:** BrCl-flav **(J)**, ClCl-flav **(K)**, 8-bromo-2,3-dehydrosilybin AB **(L)**, 6,8,21- tribromosilybin A **(M)**, 6,8,21- tribromosilybin A **(N)**, **thymol:** 4-chlorothymol **(O)**, 6-bromothymol **(P)**, 4,6-dibromothymol **(Q)**, **cinnamaldehyde:** 3-(2,4-dichlorophenyl)-1-(2-methyl-*1H*-benzo[*d*]imida-zol-1-yl)prop-2-en-1-one **(R)**, 3-(4-fluorophenyl)-1-(2-methyl-*1H*-benzo[d]imidazol-1-yl)prop-2-en-1-one **(S)**, **4-**bromocinnamaldehyde **(T)**, 3-(4-bromophenyl)-1-(2-methyl-*1H*-benzo[d]imidazol-1-yl)prop-2-en-1-one 4 **(U)**, 4-chlorocinnamaldehyde **(V)**, 4-fluorocinnamaldehyde **(W)**, and 3,4-dichlorocinnamaldehyde **(X)**.

Figure 2. Structures of halogenated alkaloids. **Indole:** CZ74 **(A),** 5-iodoindole **(B),** 5-bromotrisindoline **(C)**, 6-bromotrisindoline **(D)**, 4-fluoroindole **(E)**, 7-chloroindole **(F)**, 4′ -(4-chlorophenyl)-3′ -[(4-fluorophenyl)carbonyl]-5′ -(2-methylpropyl)spiro[indole-3,2′ -pyrrolidin]-2(1H)-one **(G)**, (3-[2-(6-bromo-2-oxo-*2H*-chromen-3-yl)thiazol-4-yl]-2-(5-chloro-2-phenyl-*1H*-indol-3-yl)thiazolidin-4-one) **(H)**, ethyl 1-(4-fluorobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-*1H*-indole-3-carboxylate **(I)**, 4-chloroindole **(J)**, 5-chloroindole **(K)**, 5-chloro 2-methyl indole **(L)**, 5-fluoroindole **(M)**, 7-fluoroindole **(N)**, ethyl 1-benzyl-5-(2-fluoro-3-(piperidin-1-yl)propoxy)-2-methyl-*1H*-indole-3-carboxylate **(O)** and ethyl 1-benzyl-5-(3-(4,4-difluoropiperidin-1-yl)propoxy)-2-methyl-*1H*-indole-3-carboxylate **(P)**, **streptochlorin:** 4-bromo-5-(*1H*-indol-3-yl)oxazole **(Q)**, ethyl 2-(3-(4-bromooxazol-5-yl)-1*H*-indol-1-yl)-2-fluoroacetate **(R)**, **quinone and quinoline:** 6-fluoro-2-methyl-*1H*-carbazole **(S)**, 6-fluoro-3-methyl-*1H*-carbazole **(T)**, 7-bromohydroxyquinoline **(U)**, 5,7-dichlorohyroxyquinoline **(V)**, 5-(2-chloroquinolin-3-yl)-3-(2,4-dichlorophenyl)-4,5-dihydro-*1H*-pyrazol-1-yl)(pyridin-4-yl)methanone **(W)**, bromoquinol **(X)**, 3-chloro-2-(5'-deoxy-1',2'-O-isopropylidene-D-xilofuranos-5'-yl)-amino-1,4- naphthoquinone **(Y)** and 3-bromo-2-(methyl-5'-deoxy-2',3'-O-isopropylidene-β-D-ribofuranosid-5'-yl)- amino-1,4-naphthoquinone **(Z)**, **4-oxoquinolizine:** 8-((3*S*,4*S*)-3-amino-4-methylpyrrolidin-1-yl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid - CC-195776 **(A1),** *(R)*-8-(7-amino-5-azaspiro[2.4]heptan-5-yl)-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid - CC-195767 **(A2)**, 1-cyclopropyl-7-fluoro-8-((4aS,7aS)-hexahydro-1*H*-pyrrolo[3,4-b]pyridin-6(2H)-yl)-9-methyl-4-oxo-*4H*-quinolizine-3-carboxylic acid - CC-195820 **(A3),** 8-(4-amino-2,5-difluorophenyl)-1-cyclopropyl-9-methyl-4-oxo-4*H*-quinolizine-3-carboxylic acid -GC-072 **(A4)**.

Figure 3. Structures of halogenated benzopyrone, phenazine and azoles derivatives. **Coumarins:** 3-(2-bromoacetyl)-2*H*-chromen-2-one **(A)**, 6-bromo-3-(2-bromoacetyl)-2*H*-chromen-2-one **(B)**, 3-(2,2-dibromoacetyl)-2*H*-chromen-2one **(C)**, 8-dibromo-*N*-4-bromo-2-fluorophenyl-2-oxo-*2H*-chromene-3-carboxamide **(D)**, 6,8-dichloro-*N*-4-bromo-2-fluorophenyl-2-oxo-*2H*-chromene-3-carboxamide **(E)**, halogenated coumarin−chalcones CC2 **(F)**, **phenazines**: 2,4-dibromo-6-chlorophenazin-1-ol **(G)**, 2,4,6-tribromophenazin-1-ol **(H)**, 2,4,8-tribromo-6-fluorophenazin-1-ol, **(I)**, 2,4-dibromo-7-(trifluoromethyl)phenazin-1-ol **(J)**, 2,4-dibromo-8-(trifluoromethyl)phenazin-1-ol **(K)**, 2-bromo-7,8-dichloro-4-iodo-5a,9a-dihydrophenazin-1-ol **(L)**, 2,4-dibromo-8-chlorophenazin-1-ol **(M)**, 7,8-dichloro-4-iodo-5a,9a-dihydrophenazin-1-ol **(N)**, 4-bromo-7,8-dichloro-5a,9a-dihydrophenazin-1-ol **(O)**, 2,4-dibromo-7,8-difluorophenazin-1-ol **(P_1)**, 1,3-dibromo-6,7-difluoroacridin-4-ol **(P_2)**, **azoles**: 1-(4-(benzo[d]thiazol-2-ylthio)-3-chlorophenyl)-3-(4-(trifluoromethyl)phenyl)urea **(Q)**, 1-(3-chloro-4-((5-chlorobenzo[d]thiazol-2-ylthio)phenyl)-3-(4-(difluorophenyl)urea **(R)**, SAR analysis for azoles **(S)**, ethyl 5-amino-1-(5-chloro-1,3-benzoxazol-2-yl)-*1H*-1–2-diazole- 4-carboxylate **(T),** ethyl 5-amino-1-(5-bromo-1,3-benzoxazol-2-yl)-*1H*-1–2-diazole-4-carboxylate **(U)**, *N*-(4-bromophenyl)-2-(4-((3-(((4-fluorophenyl)imino)methyl)phenoxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide **(V)**, *N*-(4-bromophenyl)-2-(4-((4-(((4-fluorophenyl)imino)methyl)phenoxy)methyl)-*1H*-1,2,3-triazol-1-yl)acetamide **(W)**, 3-(5-((5-(4-chlorophenyl)-6-(ethoxycarbonyl)-3-oxo-7-phenyl-3,5-dihydro-*2H*-thiazolo[3,2-a]pyrimidin-2-ylidene)methyl)furan-2-yl)benzoic acid **(X)**, -(5-((5-(4-chlorophenyl)-3-oxo-7-phenyl-3,5-dihydro-*2H*-thiazolo[3,2-a]pyrimidin-2-ylidene)methyl)furan-2-yl)benzoic acid **(Y)**, and 2-(bis((1-(3,4-dichlorobenzyl)-*1H*-1,2,3-triazol-4-yl)methyl)amino)-6-bromo-*1H*-benzo[de]isoquinoline-1,3(*2H*)-dione (Z)-3-(5-((5-(4-chlorophenyl)-3-oxo-7-phenyl-3,5-dihydro-*2H*-thiazolo[3,2-a]pyrimidin-2-ylidene)methyl)furan-2-yl)benzoate (Z)-3-(5-

((5-(4-chlorophenyl)-6-(ethoxycarbonyl)-3-oxo-7-phenyl-3,5-dihydro-*2H*-thiazolo[3,2-a]pyrimidin-2-ylidene)methyl)furan-2-yl)benzoate **(Z)**.

Figure 4. Structures of repurposed scaffolds. **Isoniazid**: 2-(2-isonicotinoylhydrazineylidene)-*N*-[4-(trifluoromethoxy)phenyl]propanamide **(A)** and *N*-(4-iodophenyl)-2-(2-isonicotinoylhydrazineylidene)propenamide (**B)**, **azo-aspirin**: 2-hydroxy-5-((2-iodophenyl)diazenyl)benzoic acid **(C),** haloperidol **(D)**, **pyrrolopyrimidine**: 4-(4-((1-(4-bromophenyl)ethyl)amino)-*7H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol **(E)** and 4-(4-((1-(4-Iodophenyl)ethyl)amino)-*7H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)phenol (**F**). SAR for pyrrolopyrimidines **(G)**, **phenothiazine:** 3,7-dibromo-10-[2-(1-methylpiperidin-2-yl)ethyl]-*10H*-phenothiazine hydrochloride **(H)**, 1,3,7,9-tetrachloro-10-[2-(1-methylpiperidin-2-yl)ethyl]-*10H*-phenothiazine hydrochloride **(I), salicylanilide:** niclosamide (**J)**, oxyclozanide **(K)**, 5-chloro-2-hydroxy-*N*-[4-(trifluoromethyl)phenyl]benzamide **(L)**, 5-bromo-2-hydroxy-*N*-[4-(trifluoromethyl)phenyl]benzamide (**M**), 5-chloro-*N*-(4'-bromo-3'-trifluoromethylphenyl)-2-hydroxybenzamide **(N)**, 5-chloro-*N*-(4′-chloro-3′-(trifluoromethyl)phenyl)-2-hydroxybenzamide **(O)**, 5-chloro-*N*-(4′-chlorophenyl)-2-hydroxybenzamide **(P)**, SAR for salicylanilides **(Q)** 5-chloro-*N*-(3,5-dibromophenyl)-2-hydroxybenzamide **(R)**, 5-chloro-*N*-(3-fluoro-4-(trifluoromethyl)phenyl)-2-hydroxybenzamide **(S)**, 5-bromo-4-chloro-2-hydroxy-*N*-[4-(trifluoromethyl)phenyl]benzamide **(T)**.

Figure 5: Structures of other halogenated bioactive compounds. **β-nitrostyrene and nitrovinylfuran:** 2-bromo-5-(2-bromo-2-nitrovinyl)furan - Furvina **(A)**, bromonitromethane **(B),** 4-bromo-β-methyl-β-nitrostyrene **(C)**, 1-fluoro-4-(nitroprop-1-enyl)benzene **(D)**, 1,3-difluoro-4-(nitroprop-1-enyl)benzene **(E)**, 2,2-difluoro-3,4-methylenedioxy-β-methyl-β-nitrostyrene **(F)**, and 4-chloro-β-nitrostyrene **(G)**, **aminothiopines:** 2-(4-chlorobenzylidene)aminothiophene-3-carbonitrile **(H)**, 2-(2,6-dichlorobenzylidene)aminothiophene-3-carbonitrile **(I)**, 2-(4-bromobenzylidene)aminothiophene-3-carbonitrile **(J)**, 6-Octanoyl-2-(2,2,2-trifluoroacetamido)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic ethyl ester **(K)**, 6-(6-bromohexanoyl)-2-(2,2,2-trifluoro-acetylamino)-4,5,6,7-tetrahydro-thieno [2,3-c] pyridine-3-carboxylic ethyl ester **(L)**, **isophthalonitrile:** 4-(benzylamino)-5-chloro-2,6-difluoroisophthalonitrile **(M)**, **β-amino amides and alboflavusins (AFN):** diamine derivative 3,5-Br-Ph **(N)**, 3,5-CF_3-Ph **(O),** diguanylated analogues 3,5-Br-Ph **(P)**, 3,5-CF_3-Ph **(Q)**, SAR for β-amino amides **(R)**, AFN 1 **(S)** and AFN 2 **(T)**.