Supporting Information for:

Inhibition of WTA synthesis blocks the cooperative action of PBPs and sensitizes MRSA to β-lactams

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Supporting Methods

Generation of ΔtarO deletion strain. CA-MRSA USA300 ΔtarO and HA-MRSA EMRSA15 ΔtarO deletion strains (EBII230 and EBII228, respectively) were generated by transduction using bacteriophage Ø11 and standard protocols (1), using the donor strain EBII44 where the chromosomal copy of tarO was previously replaced by a spectinomycin resistance cassette (2). Deletion mutants were selected for on Mueller Hinton agar containing spectinomycin (300 µg/mL). The resulting strain was confirmed by PCR.

Plasmid pLI50-tagO was generated by digestion of pSweet-tagO with HindIII and BamHI (NEB) and subsequent ligation into pLI50 cut with the same enzymes. The complemented deletion, EBII234, was generated by transformation of pLI50-tagO into EBII228 by passage through RN4220 using standard electroporation methods and selected for on MHA containing chloramphenicol (15 µg/mL) (3).

MIC determination. MIC determination was performed based on CLSI guidelines and were carried out in 200 µl in 96-well U-bottom MIC plates (VWR), in triplicate, using cation-adjusted Mueller Hinton Broth (MHB). A starting inoculum of of 10⁵ CFU/mL was used for each strain. Plates were shaken (250 rpm) and incubated at 37°C for 20 hours in and read at 600nm. The concentration where the optical density was less than 0.05 was deemed the MIC of the test compound. Fold change was calculated by dividing the MIC of the antibiotic in the parent strain by the MIC in the deletion strain.

Assembly of the PAD library. We have previously assembled a library of 1,124 previously-approved drugs from the overlap between our in-house chemical collection and compounds listed in the FDA Orange Book (http://www.fda.gov/cder/ob/) of approved drug products (4). To this subset, we have added a non-redundant subset of PADs from the Johns Hopkins Clinical
Compound Library (JHCCL, Baltimore, MD), such that the final PAD collection contains 2,080 drugs.

**Galleria mellonella survival assay.** *G. mellonella* were injected (5 µl aliquots) with 5x10⁶ cfu of live CA-MRSA USA300 bacteria using a Hamilton syringe. Following bacterial cells, cefuroxime, ticlopidine and their combination (dissolved in water) were administered in 2 µl aliquots. Five control groups were used, including untreated larvae, larvae injected with saline, water and their combination, and larvae injected with saline and cefuroxime, ticlopidine and their combination. For each treatment, a group of at least 10 larvae were injected. Experiments were repeated 3 independent times with different batches of larvae and the results averaged. Larvae were left at room temperature and scored as dead or alive every 24 hrs for 14 days.

**Interaction studies of ticlopidine with antibiotics of known mechanism.** 8x8 matrices of ticlopidine in combination with various known antibiotics were tested for interactions against CA-MRSA USA300 using the same conditions as screening. FIC indexes were calculated to evaluate the interactions.

**TarO expression.** *tarO* optimized for expression in *E. coli* and inserted into pBAD24 was obtained from GenScript. Empty vector or pBAD24-*tarO* was transformed into *E. coli* BW25113 ΔwecA from the KEIO collection (5) for protein expression. An overnight culture was diluted 1/100 into fresh LB and incubated at 37 °C, 250 rpm until cultures reached an OD of 0.4. Protein expression was induced with 2 % (w/v) arabinose and incubated for 3 hrs under the same conditions. Cells were harvested by centrifugation (10 minutes, 8 000 x g), washed with 0.85% NaCl and stored at -80 °C overnight. Frozen cell pellets were thawed in an equal volume of lysis buffer (50 mM Tris pH = 8, 10 mM MgCl₂, 1 mM EDTA, 100 µg mL⁻¹ DNase, 100 µg mL⁻¹ RNase, 1 protease inhibitor cocktail tablet (Roche)), and lysed with a One Shot Cell Disruptor.
(Constant Systems Ltd.). Lysate was clarified by centrifugation (40,000 x g, 15 minutes). Membranes were recovered from the supernatant of the previous step by ultracentrifugation (111,000 x g, 60 min) and resuspended in Reaction Buffer (50 mM Tris pH = 8, 10 mM MgCl₂, 1 mM EDTA) to a final concentration of approximately 60 mg membrane protein/mL (as determined by the Bradford method).

**Generation of a tarH conditional deletion strain.** To create a xylose-dependent tarH conditional strain (EBII244), the xylose repressor encoded by xylR and the xylA promoter were first subcloned from pSWEET-tarD into the MfeI and BamHI sites of pCL55 to generate pCL55-tarD. tarH was amplified from pG164-tarH (EBII10) with primers # (5' - GGGCTTAATTAAAGGAAGGTTCTACAAATGAACGTTTCGGTAAACA - 3') and # (5' - GGGCGGATCCGTTTAAACTCGAGCGGCCGCTTATTTAATAACGA - 3') and cloned into the PacI and BamHI sites of pCL55-tarD to generate pCL55-tarH. All inserts were verified by sequencing (MOBIX, McMaster University, Hamilton, ON). pCL55-tarH was then transformed into EBII4 using standard electroporation methods and selected for on MHA containing chloramphenicol (15ug/mL) and kanamycin (20ug/mL). Integration of pCL55-tarH into the geh locus of EBII4 was confirmed by PCR. This tarH single integrant strain was then passaged three times on MHA containing 5% sucrose, 2% xylose and erythromycin (10ug/mL). The resultant conditional tarH deletion strain (EBII244) was confirmed by PCR and tested for xylose-dependence by streaking on MHA plates with or without 2% xylose.

**Phage susceptibility.** Strain *S. aureus* RN450 was grown to exponential phase in the presence of compounds, plated and incubated with bacteriophage 11. Plates were incubated for 24 hours at 37°C.
Peptidoglycan isolation and lysozyme susceptibility. Cell wall samples from ticlopidine-treated cells and CA-MRSAUSA300 ΔtarO were treated with 48% hydrofluoric acid at 4°C for 24 hours. Peptidoglycan was harvested by centrifugation at 30,000 rpm for 30 minutes and washed twice with water. Peptidoglycan was incubated in 80mM NaOH at 37 °C for 3 h, spun and resuspended in 80 mM sodium phosphate buffer/0.85% NaCl (pH 6.5) to similar optical densities. Peptidoglycan was digested with 300 µg/mL chicken egg white lysozyme (Sigma-Aldrich). The decrease in the absorbance at OD600 nm was monitored at 30-min intervals for 6 hrs using a Sunrise plate reader (Tecan).

TarA and MnaA expression and purification. Expression and purification of TarA and MnaA as previously described(6).

In vitro TarA inhibition assay. TarA was assayed in 50 uL reactions containing 50 mM tris (pH 8), 250 mM NaCl, 2% DMSO, 0.2% TX-100, 0-1.7 mM Ticlopidine, 200 uM lipid α, 50 nM TarA, and 4 uM MnaA. MnaA was added to the assay to catalyze the isomerization of UDP-GlcNAc to the TarA substrate, UDP-ManNAc. Reactions were initiated by the addition of 200 uM UDP-GlcNAc and terminated with the addition of 50 uL of 8 M urea. Reaction products were separated and quantified by PIC-HPLC, as reported previously(6)
Supplementary Figure 1. Chemical structure of a completed wall teichoic acid polymer from *S. aureus* bound to N-acetylmuramic acid of peptidoglycan. PBP transglycosylase domains catalyze the polymerization of disaccharide units composed of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG). Adjacent peptide stems are cross-linked by the transpeptidase function of PBPs to provide the cell wall polymer with its structural integrity. Attached at the 6-hydroxyl of NAM is a completed WTA polymer, composed of \((n = 1-3)\) glycerol phosphate and \((m = 20-40)\) repeating ribitol phosphate units that are modified by D-alanine (D-ala) and N-acetylglucosaminyl residues (GlcNAc).
Supplementary Figure 2. Highly cross-linked muropeptides, contributed by PBP4, are less abundant in MRSA ΔtarO deletion strains. (a) HPLC analysis of mutanolysin-digested PG of the parental strains HA-MRSA EMRSA15, CA-MRSA USA300, their ΔtarO deletions and the complemented deletion strain, HA-MRSA EMRSA15ΔtarO pLI50-tagO. Arrow points to highly crosslinked muropeptide species. Roman numerals I to V indicate muropeptide species form monomers to pentamers. (b) Quantification of highly cross-linked muropeptides (peaks > V) from the HPLC analyses. The values denote a representative analysis and variations in sample concentration were corrected for by calculating the areas for each peak and dividing the obtained values by the total area of the chromatogram.
**Supplementary Figure 3.** Screen of a previously-approved drug library to uncover molecules that potentiate the activity of cefuroxime as potential inhibitors of WTA synthesis. (a) Replicate plot of the primary screening results. CA-MRSA USA300 was grown with one eighth the MIC of cefuroxime (16 µg/mL) and each of the 2,080 PAD compounds at 10 µM. Shown are the ratios of the growth of the combinations normalized to the growth of the PADs alone of replicate samples (RI and R2). In red are statistically significant hit molecules with a ≤0.7 cutoff. (b) Schematic diagram of the work flow of the screen conducted from 2,080 compounds to the lead molecule, ticlopidine. Compounds were eliminated at each stage according to the criteria indicated. Specifically, after confirming synergistic interactions among the compounds and cefuroxime in a checkerboard analysis, the various combinations were tested in CA-MRSA USA300 ∆tarO to look for suppression. Only the synergy between ticlopidine and cefuroxime was completely suppressed in the deletion strain.
Supplementary Figure 4. Microdilution checkerboard analysis showing the combined effect of targosil and ticlopidine against *S. aureus* RN4220 where the extent of inhibition is shown as a heat plot. Ticlopidine antagonizes the effect of targosil, a WTA late-step inhibitor.
Supplementary Figure 5. Ticloididine-treated *S. aureus* SA178R1 cells have decreased phosphate content in their cell wall.
Supplementary Figure 6. Ticlopidine-treated cells are less susceptibility to phage infection. Strain *S. aureus* RN450 was grown to exponential phase in the presence of ticlopidine (200µg/mL) and tunicamycin (0.025 µg/mL), plated and incubated with bacteriophage Ø11. Plates were incubated for 24 hours at 37°C.
Supplementary Figure 7. Peptidoglycan derived from ticlopidine-treated cells is more susceptible to degradation by lysozyme. Shown is the hydrolysis of purified PG from CA-MRSA USA300 (circles), CA-MRSA USA300 ΔtarO (squares) and ticlopidine (200 µg/mL)-treated CA-MRSA USA300 (triangles) followed by monitoring the decrease in OD$_{600}$ nm over time.
Supplementary Figure 8. Validation of \textit{in vitro} assay for TarO activity. Assay was validated by showing incorporation of [14C]GlcNAc from UDP-[14C]GlcNAc into lipid extractable material. Generation of the reaction product (likely undecaprenyl-P-P-[14C]GlcNAc) was shown to be dependent on expression of TarO from pBAD24 expression plasmid. No lipid-linked radioactive species were observed from the cells harboring empty pBAD24 plasmid.
**Supplementary Figure 9.** Assay of TarA activity in the presence of ticlopidine. No inhibition was observed on the transferase activity of TarA with increasing concentrations of ticlopidine.
Supplementary Table 1. Cell wall phosphate analysis of CA-MRSA USA300 and HA-MRSA EMRSA 15 strains and their ΔtarO deletion strains.

| Strain                                          | µmol phosphate / mg cell wall |
|------------------------------------------------|-------------------------------|
| CA-MRSA USA300                                  | 0.430 ± 0.040                 |
| CA-MRSA USA300 ΔtarO                            | 0.085 ± 0.009                 |
| HA-MRSA EMRSA15                                 | 0.300 ± 0.050                 |
| HA-MRSA EMRSA15 ΔtarO                           | 0.035 ± 0.007                 |
| HA-MRSA EMRSA15 ΔtarO – pLI50-tagO              | 0.307 ± 0.03                  |
### Supplementary Table 2. Components of the PAD Library.

| Chemical Name                        | Chemical Name                        | Chemical Name                        |
|--------------------------------------|--------------------------------------|--------------------------------------|
| Tinoridine hydrochloride             | Proxpyphylline                        | Procainamide hydrochloride           |
| Thioctic acid amide                  | Levobunolol                           | Ethnynyl Estradiol                   |
| Flufenamic acid aluminium            | Doxazosin                             | Estrone Sodium Sulphate              |
| Todralazine hydrochloride            | Phthalylsulfathiazole                 | Ammonium carbonate                   |
| Imipramine                           | Nizatidine                            | Guaiacol                             |
| Sulindac                             | Propranolol                           | Levopropoxyphene napsylate           |
| Atracurium                           | Metyparone                            | Brompheniramine (\(\pm\))-           |
| Cimetidine                           | Cloroquinol                           | Norepinephrine                       |
| Doxylamine                           | Flurbiprofen                          | Moexepril                            |
| Dicyclomine                          | Timolol                               | Strophanthidin                       |
| Methaqualone                         | Methylatropine                        | Acarbose                             |
| Sodium glucuronate                   | Levbunolol                            | Insulin aspart                       |
| Ambroxol hydrochloride               | Acetaminophen                         | Hydroxyprogesterone acetate          |
| Allantoin                            | Capsaicin                             | Methoxyfenamine                      |
| Acetazolamide                         | Propofol                              | Nedocromil sodium                    |
| Metformin                            | Felbinac                              | Guaiacol                             |
| Heptaminol                           | Estrone                              | Emedastine difumarate                |
| Troleandomycin                        | Fluspirilene                          | Carteolol hydrochloride              |
| Pyrimethamine                        | Prazosin                              | Nicotinyl alcohol                    |
| Oxethazaine                          | Nabumetone                            | 6-Aminocaproic acid                  |
| Sodium succinate                     | Protriptyline                         | Carbazochrome                        |
| Xanthinol niacinate                  | Aminocaproic acid                     | Iodine resublimed, p.a.              |
| Chlorphenesin                         | Alfaxalone                            | L-Thyroxine                          |
| Benzonatate                          | methacycline hydrochloride            | (1R,2S)-(-)-Ephedrine                |
| Hydroflumethiazide                    | Letrozole                             | Acrivastine                          |
| Sulfacetamide                        | Etilefrine                            | Dimethindene (S, +) maleate          |
| Thiamphenicol                         | methyl dopate hydrochloride           | Terpin                               |
| Naphazoline                          | Lymecycline                           | Ergoloid mesylate                    |
| Ticlopidine                           | Propranolol                           | Nisoldipine                          |
| Isoxsuprine                          | Adenosine                             | Hetastarch                           |
| benzyl mandelat                      | Prednicarbate                         | Heparin                              |
| tegafur                              | Remoxipride                           | Ibandronate                          |
| Meticrane                            | Trapidil                              | Cromolyn                             |
| Panthenol                            | Cyclophentiazide                      | Zafirlukast                          |
| Sulfadiazine                         | Molindone                             | trans-Anethole                       |
| Norethynodrel         | Tocainide          | Bromodiphenhydramine hydrochloride |
|-----------------------|-------------------|-----------------------------------|
| Dapsone               | ozagrel sodium    | Fexofenadine hydrochloride        |
| Sulpiride             | Talamipicillin    | Mebutamate                        |
| Oxybuprocaine         | Spaglumic acid    | Amyl Nitrate inhalant             |
| Thioridazine          | Loracarbef        | Coumarin                          |
| quinine ethylcarbonate| Cyproterone        | Fondaparinux sodium               |
| naphazoline hydrochloride | Gliquidone     | Pravastatin sodium                |
| Sulfaphenazole        | Articaine         | Ibutilide fumarate                |
| epirizole             | meptazinol        | Tolonium chloride                 |
| Diprophylline         | Sotalol           | Ipecac syrup                      |
| Triamterene           | Zalcitabine       | Magnesium chloride 6-hydrate      |
| Naproxen              | Proguanil         | Methyl-cellulose                  |
| Minaprine             | Rimexolone        | Calcium carbonate                 |
| Miconazole            | Netilmicin        | Potassium bitartrate              |
| Hydrochlorothiazide   | Procarbazine      | Magnesium hydroxide               |
| mesulfen              | Natamycin         | D-Sorbitol                        |
| indoramin             | Fluoxacillin      | Methyclothiazide                  |
| Chloramphenicol       | Ribavirin         | Anagrelide hydrochloride          |
| Moxisyltye            | Sertraline        | Glycocyamine                      |
| Betazole              | Proscillaridin    | Aluminum acetate, basic           |
| Mefenamic acid        | Mecamylamine      | Sodium bicarbonate, powder        |
| Acetohexamide         | Pivampicillin     | Bismuth(III) citrate              |
| Dibucaine             | Torasemide        | Bismuth(III) oxide                |
| Prednisone            | Mecamylamine      | Magnesium carbonate               |
| Captopril             | Penbutolol        | Aprepitant                        |
| oxycinchophen         | Saquinavir        | Potassium sodium tartrate         |
| clomipramine hydrochloride | Isradipine       | tetrahydrate                      |
| Procaine              | Azapropazone      | Cholesterylamine resin            |
| Carbamazepine         | Nifurtimox        | Oxalic acid dyhydrate             |
| Trifluromazine        | epitiostanol      | Sodium taurocholate hydrate       |
| Chlorpromazine        | Memantine         | Aloe                              |
| Diphenhydramine       | Tribenoside       | Bismuth subcarbonate              |
| Amiloride             | Pyrvinium         | Benzyl alcohol                    |
| Idoxuridine           | Tridihexethyl     | Dimenhydrinate                    |
| antipyrine            | Pivmecillinam     | Calcium hydroxide                 |
| efloxate              | Sertaconazole     | Potassium sulfate                 |
| cyclobutylor          | Halofantrine      | Safflower oil                     |
| trichlorfon           | Deptropine        | Esmolol                           |
| Homatropine         | Pancuronium | Metipranolol       |
|--------------------|-------------|--------------------|
| Nifedipine         | Moxonidine  | Karaya powder      |
| nortriptyline      | Zuclopenthixol | Bismuth subnitrate |
| Sulfathiazole      | Risperidone | Misoprostol        |
| Levodopa           | Etomidate   | Castor oil         |
| Ethambutol         | Iopanoic acid | Prochlorperazine dimaleate salt |
| Diflunisal         | Naftifine   | Docusate sodium    |
| Pheniramine        | Piperidolate | Edetate calcium disodium |
| Tolnaftate         | Rilmenidine | Phenoxyacetic acid |
| zimeldine          | Isomethyptene | Cilostazol        |
| Ciprofloxacin      | naftopidil  | Citric acid        |
| Ampicillin         | Fluticasone | Bismuth (III) phosphate |
| Haloperidol        | Alprostadil | Sodium bismuthate  |
| Naltrexone         | Levocabastine | Bismuth III gallate basic hydrate |
| Isoconazole        | Moricizine  | Difenidol hydrochloride |
| Spironolactone     | Ioxaglic acid | Pantoprazole      |
| Pindolol           | Bethanechol | Potassium phosphate monobasic |
| Acebutolol         | Milrinone   | Succimer           |
| Trimethobenzamide  | Pizotifen   | Clofibrate         |
| Amoxapine          | Nomegestrol | DL-Carnitine hydrochloride |
| dehydrocholic acid | Fluvoxamine | Ethoxozalamide     |
| Hesperetin         | fursultiamin | Benzyl salicylate  |
| Perphenazine       | Benzathine benzylpenicillin | Esomeprazole   |
| Mefloquine         | Pirbedil    | Zinc oxide         |
| Clindamycin        | Phensuximide | Prochlorperazine dimaleate |
| Terfenadine        | Lansoprazole | Calamine           |
| Acenocoumarol      | viomycin sulfate | Magnesium oxide   |
| Diphenanil         | Propranolol  | Nalmefene          |
| Metronidazole      | Cyclopentolate | 3-hydroxytyramine  |
| Metolazone         | Meropenem   | Dopamine           |
| Hydroxyzine        | Ondansetron | Zinc acetate       |
| Diltiazem          | Chlorambucil | Witch hazel        |
| Methotrexate       | Vitamin K   | Zinc chloride      |
| Astemizole         | Prostaglandins | Casanthranol      |
| Nicergoline        | vinorelbine  | Boric acid         |
| Neomycin           | chlorpheniramine | Danthron        |
| Triamcinolone      | efornithine hydrochloride | Dolasetron mesylate |
| Sulfaguanidine     | Fenoldopam   | Perflubron         |
| Compound                      | Compounds                                | Compound                          |
|-------------------------------|------------------------------------------|-----------------------------------|
| Apomorphine                   | Verteporfin                              | Potassium nitrate                 |
| Loxapine                      | Dorzolamide                              | Torsemide                         |
| Chlorhexidine                 | Thiethylperazine                         | Magnesium peroxide                |
| Loperamide                    | Cycloserine                              | Taurocholic acid, sodium salt hydrate |
| Chlortetracycline             | Cyclacillin                              | Carboxymethyl-cellulose           |
| Tamoxifen                     | Prostaglandins                           | Olive oil                         |
| Gallamine                     | Metyroline                               | Croton oil                        |
| mianserin                     | cortisone acetate                        | Potassium phosphate dibasic       |
| Dexamethasone                 | Enoximone                                | Gallic acid                       |
| Minoxidil                     | Flupirtine                               | Oleic acid                        |
| Naloxone                      | Repaglinide                              | Magnesium acetate                 |
| Dipyridamole                  | Piretanide                               | Senna syrup                       |
| Midecamycin                   | Benzylpenicillin                         | Iofetamine                        |
| Josamycin                     | Nialamide                                | L-Arginine hydrochloride          |
| Paclitaxel                    | mithramycin                              | Potassium bicarbonate, granular    |
| Ivermectin                    | Prostaglandins                           | Seleno-D, L-methionine            |
| aminopyrine                   | apraclonidine hydrochloride              | Beclamide                         |
| Pirenzepine                   | meclofenoxate hydrochloride              | Lithium bromide                   |
| Tetracycline                  | Epinephrine                              | Quetiapine fumarate               |
| Niclosamide                   | Formoterol                               | 4-Aminobenzoic acid               |
| Glipizide                     | Trifluridine                             | Psyllium husk                     |
| Oleandomycin                  | Oxprenolol                               | Hexadimethrine bormide            |
| moroxydine                    | oxedrine                                 | Glucose (D)                       |
| Baclofen                      | Rifabutin                                | Basic fuchsin hydrochloride       |
| acyclovir                     | Artesunate                               | D-Xylose                          |
| Diazoxide                     | Prostaglandins                           | Sodium Thiosulfate                |
| Acetylsalicylic acid          | gamma-aminobutyric acid                  | Escitalopram oxalate              |
| Cefotaxime                    | stavudine                                | Phenytoin                         |
| Dihydroergotamine             | Epinephrine                              | Sertraline hydrochloride          |
| lidocaine                     | flupenthixol                             | Dichlorophenamide                 |
| verapamil                     | Methantheline                            | Ethylenediaminetetraacetic acid   |
| Edrophonium                   | Ticarcillin                              | Phenolsulfonphthalein             |
| Azathioprine                  | Mephenytoin                              | L-Arginine L-glutamate salt       |
| Lynestrenol                   | Clocortolone                             | Sodium diatrizoate                |
| guanabenz acetate             | Cerulenin                                | Meglumine diatrizoate             |
| Disulfiram                    | Prostaglandins                           | Glycerin (Glycerol)               |
| Nomifensine                   | calcium l-aspartate                      | Paramethadione                    |
| Thioproperazine               | doxylamine succinate                     | Lithium salicylate                |
| Drug Name          | Chemical Formula                        | Description               |
|--------------------|-----------------------------------------|---------------------------|
| Isoniazid          | polyestradiol phosphate                 | Biperiden hydrochloride   |
| Tolazoline         | Glutamic acid hydrochloride             | DL-homatropine            |
| Erythromycin       | Ciprofibrate                            | Tiopronin                 |
| Cyproheptadine     | Isoprenaline                            | Sodium phosphate dibasic  |
| Famotidine         | Cefepime                                | Copper (II) sulfate       |
| Danazol            | Quinethazone                            | Mebrofenin                |
| Lisuride           | Fumagillin                              | Chymopapain               |
| chlorpheniramine   | Cefradine                               | Disofenin                 |
| Nalbuphine         | Amsacrine                               | Lithium benzoate          |
| Dihydrostreptomycin| Clodronic acid                          | Meprobamate               |
| Tranexamic acid    | Felbamate                               | Tri-lithium citrate       |
| Midodrine          | Levoglutamid                            | Calcium bromide           |
| Tiratricol         | Cycloserine                             | Sodium polystyrene        |
| Xylometazoline     | Ramipril                                | L-Arginine                |
| Oxymetazoline      | Oxypenbutazone                          | Pentagastrin              |
| Mafenide           | Oxaprozin                               | Sodium iodide             |
| Rituzole           | Sirolimus                               | Trientine                 |
| Salbutamol         | Silymarin                               | Magnesium sulfate         |
| Metoclopramide     | benztrapine mesylate                    | DL-Glutamic acid monohydrate |
| Indapamide         | gadopentetate dimeglumine               | Fosphenytoin sodium       |
| Dantrolene         | fenoterol hydrobromide                  | Acetophenazine maleate    |
| Ranitidine         | gallamine triethiodide                  | Dioxybenzone              |
| Pyrantel           | Estriol                                 | Fluorescein               |
| Hyoscyamine        | piperacetazine                          | Ethanol                   |
| chlorphenesin carbamate | mesalamine                      | Sodium chromate           |
| Iproniazide        | santonin                                | Sodium sulfate, powder    |
| Sulfamethoxazole   | Prostaglandins                          | Evans blue                |
| Trimethoprim       | rutosid                                 | Mirtazapine               |
| Ketoprofen         | ubenimex                                | Phenacemide               |
| Phentolamine       | doxazosin mesylate                      | Strontium bromide hexahydrate |
| Lisinopril         | Flumazenil                              | Dipivefrin HCl           |
| Piroxican          | oxiriptan                               | L-Phenylephrine hydrochloride |
| Chlorzoxazone      | Ibutilide                               | Bentiromide               |
| Ornidazole         | levallorphan tartrate                   | Fomepizole                |
| Ethosuximide       | Metyrosine                              | Rubidium iodide           |
| Cloxacillin        | protoporphyrin disodium                 | Protamine chloride, grade V |
| Nalidixic acid     | Butylscopolamine                        | Zoxazolamine              |
| Fenbufen           | tropisetron                             | Selegiline                |
| Nefopam | desoxycorticosterone acetate | Nicotine |
|---------|-----------------------------|---------|
| Proglumide | methicillin | Iproniazid |
| Ifenprodil | Bromhexine | Ammonium bromide |
| Norfloxacin | pseudoephedrine | Bemegride |
| Tranylcypromine | Ipratropium bromide | Inulin |
| Alverine | Linopirdine | Rose bengal |
| Aceclofenac | Methysergide | Sodium phosphate monobasic |
| Pentoxifylline | Picotamide | Lidofenin |
| Metaraminol | Succinylcholine | Metrizoic acid |
| Tropicamide | tropisetron | Molindone hydrochloride |
| Orphenadrine | levomenol | Benztropine Methane-Sulfonate |
| Metaraminol | suramin hexasodium | Olsalazine |
| Lomefloxacin | terguride | Auranoxin |
| Phenelzine | xylitol | Stanozolol |
| Chlorothiazide | Methylthiouracil | Betamethasone 21-acetate |
| Diphenidol | Amcinonide | Pyroxylin |
| pentylenetetrazol | Thiamylal | Vitamin A (acetate) |
| Oxolinic acid | isoproterenol | Menthol salicylate |
| Nimesulide | metaproterenol | Frovatriptan succinate |
| Tolfenamic acid | Oxiracetam | Flurothyl |
| Tiapride | sodium prasterone sulfate | Nikethamide |
| Ofloxacin | tranilast | Desonide |
| Hydralazine | brimonidine | Dexamethasone phosphate |
| Flutamide | alpha tocopherol acetate | Colloidal oatmeal |
| Ethisterone | Salicylamide | Cyclosporin A |
| Triprolidine | Hydroxychloroquine | D-Pantothenic acid calcium salt |
| Levamisole | Sodium salicylate | Menadiol disulfate |
| Flufenamic acid | Iodine iofetamine | Lantanoprost |
| Flumequine | compactin | Akwa tears |
| Nifenazone | Oxatomide | 2,2,2-Trichloroethanol |
| Griseofulvin | Ropinirole | Acetal |
| Nitrofurantoin | aminoethylsulfonic acid | Corticotropin A |
|---------------|-------------------------|----------------|
| Phenformin    | Xanthines               | Benzoyl peroxide |
| Tolbutamide   | Acetylcholine           | Malathion       |
| Vincamine     | Acetarsol               | Deoxyribonuclease I |
| Indomethacin  | Teniposide              | Riboflavin      |
| Thalidomide   | Phenolphthalein         | Alanine, D, L  |
| Fenspiride    | Ioxoprofen sodium       | Caffeine citrate |
| Gemfibrozil   | Mibebradil              | Choline dihydrogen citrate |
| Metampicillin | pentolinium             | Magnesium bromide |
| Dilazep       | Ranolazine              | Potassium bromide |
| Mephenesin    | sapropterin hydrochloride | Arbutin         |
| Prilocaine    | Zonisamide              | Hydroxypropyl cellulose |
| Fenbendazole  | Ephedrine               | Fluocinolone acetonide 21-acetate |
| Fludrocortisone | Ursodeoxycholic acid | Methoxsalen     |
| Fenoterol     | Mepivacaine             | Vitamin D2      |
| Trazodone     | Ephedrine               | Selenium sulfide |
| Glafeanine    | Lamotrigine             | Strychnine      |
| Econazole     | gallopamil              | Donepezil hydrochloride |
| Bupivacaine   | Valproic acid           | Atropine sulfate |
| Clemastine    | sobuzoxane              | Eletriptan hydrobromide |
| Oxytetracycline | Atomoxetine            | Esculin monohydrate |
| Pimozide      | Chenodeoxycholic acid   | Nandrolone decanoate |
| amodiaquin    | flumethasone            | Pimecrolimus    |
| Streptomycin  | cefoperazone sodium     | Aluminum chlorohydrate |
| Practolol     | Aminolevulinic acid     | Acetic acid     |
| Lincomycin    | retinol                 | Calcium L-ascorbate dihydrate |
| Trifluoperazine | Lonidamine            | Ergotamine D-tartrate |
| Enalapril     | cysteamine              | Sulisobenzene   |
| Minocycline   | Mepyramine              | Rugby artificial tears solution |
| Glibenclamide | denopamine              | 21-Acetoxypregnenolone |
| Guanethidine  | Trifluperidol           | Azaribine       |
| Quinacrine    | hydroxyamphetamine hydrobromide | Calciopotiene |
| Alpranolol    | Lactulose               | Allyl isothiocyanate |
| Flurosemide   | Acetylcarnitine         | Dichlorisone acetate |
| Methapyrilene | avobenzene             | Retinoic acid   |
| Flunarizine   | Edoxudine               | Ferrous bromide |
| Glutethimide  | Cymarin                 | Octyl Methoxyxinnamate |
| Dropropizine  | Busulfan                | 1,2-Ethanedisulfonic acid |
| Pinacidil     | sodium edetate      | Modafinil          |
|--------------|---------------------|--------------------|
| Albendazole  | Digitoxin           | Hydrocortisone hemisuccinate |
| Clonidine    | Oxacillin           | Ethylamine         |
| Bupropion    | Tuaminoheptane      | Flumethasone pivalate |
| Praziquantel | Mesna               | Methdilazine hydrochloride |
| chlorthalidone| Dibekacin           | Methyl nicotinate  |
| Dobutamine   | Oxyphencyclidine    | Ferric phosphate   |
| Bufexamac    | Clarithromycin      | Stannous fluoride (Tin(II) fluoride) |
| Nortriptyline| Acetohydroxamic acid| Latanoprostone ophthalmic solution |
| Niflumic acid| Carbencilllin       | Lithium carbonate  |
| Isotretinoin | Ethinylestradiol    | Acecarbromal       |
| alitretinoin | diiodohydroxyquinoline| Aminopyrine        |
| Antazoline   | Oxyquinoline        | Meloxicam          |
| Ethacrynic acid| Tyrothricin       | Triamcinolone acetonide acetate |
| Fendiline    | Foscarnet           | Phenylbutazone     |
| Bambuterol   | Cetrimonium         | Methyl salicylate  |
| Betamethasone| Pericazine          | Sodium ferric gluconate |
| Norgestrel   | Rofecoxib           | Vitamin A acetate  |
| Dyclonine    | Aminosalicylic Acid | Allantoic acid     |
| dimenhydrinate| Cetylpyridinium     | Indium(III) chloride |
| Disopyramide | gentian violet      | Peruvian balsam    |
| Clotrimazole | Mechloretamine      | Cholecalciferol    |
| Vinpocetine  | Penicilllin G       | a-Casein dephosphorylated |
| Clomipramine | Broxyquinoline      | Diethyl oxalate    |
| Quinidine    | cephaloridine       | Dibutyl phthalate  |
| Ketotifen    | Chloroxine          | Ethohexadiol       |
| Betaxalol    | sennoside           | Human immunoglobulin |
| Doxepin      | Oxcarbazepine       | Hycanthone         |
| Prednisolone | Amodiaquine         | Niacinamide hydrochloride |
| Fenofibrate  | chlorocrresol       | Vitamin K3         |
| Bumetanide   | Glucosamine         | Chromium (III) chloride |
| Labelalol    | Medroxyprogesterone | Podophyll resin    |
| Cinnarizine  | pseudoephedrine     | Cevimeline hydrochloride |
| Methylprednisolone| guanidine          | Potassium citrate monohydrate |
| Sulfinpyrazone| Anisindione         | Orotic acid        |
| Lidoflazine  | Clofoctol           | Oxytocin           |
| Ketanserin   | Phenothrin          | Pyrethrins technical mixture |
| Cortisone    | Carvedilol          | Toltrazuril        |
| Compound | Compound | Compound |
|----------|----------|----------|
| Diethylcarbamazine | anthralin | Sodium formate |
| Chenodiol | Chloroxylenol | Pyridoxine hydrochloride |
| Perhexiline | Hetacillin | Zinc sulfide |
| Oxybutynin | Methenamine | Neovitamin A |
| Spiperone | Piperazine | Disulfiram |
| Pyrilamine maleate | Iodamide meglumine | Ferrous gluconate hydrate |
| Mebeverine | Glutathione | Drospirenone and ethinyl estradiol |
| Terbutaline | Thiotepa | Bismuth subsalicylate |
| Chlorpropamide | Sildenafil | Ethylenediamine dihydrochloride |
| Homochlorcyclizine | Nateglinide | Lomofungin |
| Pimethixene | Benztpine | Hydroxocobalamin hydrochloride |
| Pergolide | Dexchlorpheniramine | Inositol |
| Acemetacin | Hexachlorophene | Riboflavin phosphate sodium |
| Benzydamine | Nafcillin sodium | Vitamin B12 |
| Fipexide | Pseudoephedrine | Ferric sulfate heptahydrate |
| Mifepristone | Glycyr rhetic acid | Chloropheno therapy |
| Fluphenazine | Gamma-amino-beta-hydro | Ferrous sulfate |
| Alfuzosin | Semustine | Vardenafil |
| Zidovudine | Venlafaxine | Methylene blue hydrate |
| Desipramine | Irbesartan | Bifonazole |
| Metergoline | Beta-carotene | Vitamin B4 |
| Amikacin | Colistimethate | Ammonium lactate |
| Cefoperazone | Hexylresorcinol | Picric acid |
| Bezafibrate | Norethindrone acetate | Cod liver oil |
| Mimosine | Resorcinol | Butopyronoxyl |
| Clebopride | Retinol | Dinoprostone tromethamine |
| Cefixime | Flocuridine | Dimethyl phthalate |
| Ciclosporin | Celecoxib | Potassium ricinoleate |
| Digoxin | Acrisorcin | Ferric ammonium citrate |
| Enoxacin | Levofoxacin | Ethacridine lactate |
| Methylergometrine | Bithionol | alpha-D-Lactose monohydrate |
| Methyldopa | Pyrithione zinc | Permethrin |
| Procanamide | Hydroxyprogesterone | Zirconium(IV) oxide |
| Dequalinium | Orphenadrine citrate | Potassium hydroxide |
| Ketoconazole | Thioguanine | Ferrous fumarate |
| Fusidic acid | Carprofen | Sodium ethasulfate |
| d-thyroxine | Quinapril | Ursodiol |
| Cyclobenzaprine | Azithromycin | Doxapram hydrochloride |
| Hydrocortisone | Metaxalone | Acetylcysteine |
|----------------|------------|----------------|
| Colchicine     | candesartan| Flubendazole   |
| Probucol       | Rosiglitazone| Sodium hydroxide |
| Chloromezalone | Famciclovir| Magnesium phosphate hydrate |
| Amoxicillin    | Situbramine| Cobalamin concentrate |
| Oxantel        | adenine    | Ammonium magnesium phosphate hydrate |
| Prochlorperazine| Ipriflavone| Butyl paraben  |
| Testosterone    | Telmisartan| Rutin trihydrate |
| Carisoprodol   | erythromycin gluceptate| Tadalafil |
| Brompheniramine| 2h-1-benzopyran-2-one| Dimethyl sulfoxide |
| Meclozine      | Albuterol  | Cevimeline     |
| methotrexate   | Divalproex | Metrifonate    |
| Kanamycin      | Losartan   | Calcium phosphate tribasic |
| Maprotiline    | Amiodipine | Zinc stearate  |
| Benfluorex     | Perindopril| Nadide         |
| Tacrine        | cholesterol| Ergosterol     |
| Bisoprolol     | chlorophenothane| Dodecylamine |
| mesterolone    | cholesterol| Ferrous lactate |
| Cyanocobalamin | Polymyxin B| Iron(II) sulfate heptahydrate |
| Bacampicillin  | sodium phenylbutyrate| Simethicone |
| Progesterone   | demeclocycline hydrochloride| Butyl chloride |
| Nicardipine    | Hematin    | Symclosene     |
| Ascorbic acid  | Gatifloxacin| Cephalosporin c |
| Adenosine      | Ezetimibe  | Mepartricin    |
| clomiphene     | Rosuvastatin| Trilokaran   |
| Guanfacine     | I-glutamine| Protionamide   |
| Flupentixol    | Pikrinic acid| Penimepicycline |
| Sultovalidil   | Thiram     | Docosanol      |
| Metrizamide    | Hydroxyprogesterone| Carzenide |
| Buflomedil     | epidihydrocholesterin| Bucetin |
| Butoconazole   | clomiphene citrate| Salicin |
| Phenylpropanolamine | Mebhydrolin| Cotinine |
| Clenbuterol    | Valdecoxib | Rufloxacin HCl |
| Ambroxol       | Almotriptan| Oxibendazole   |
| Chlorprothixene| Tegaserod  | Phenothiazine   |
| Ritodrine      | Tolperisone| Pazufloxacin   |
| Clozapine      | Dactinomycin| Nifursol       |
| Estradiol      | Pipobroman | Tetramisole    |
| Cefotetan       | Warfarin       | Rifaximin       |
|----------------|----------------|-----------------|
| Carteolol      | Benzyl benzoate| Pravadoline     |
| Biotin         | sodium cromoglicate| Polidocanol     |
| Sulfisoxazole  | meclocycline sulfosalicylate | Idazoxan hydrochloride |
| Brinzolamide   | Moxifloxacin   | Climbazole      |
| Clofazimine    | Olmesartan medoxomil | Clorsulon      |
| Cephalexin     | Troxerutin     | Clofazimine     |
| Dextromethorphan| Inosine        | Sulfanilate Zinc|
| Droperidol     | Thiopental     | Zanamivir       |
| Domperidone    | anethol        | Diclazuril      |
| tocopherol     | flopropione    | Benzododecinium chloride |
| Meclocycline   | Aminophenazone | Lidocaine N-ethyl bromide |
| Doxorubicin    | Gentamicin     | 5-hydroxy-DL-Tryptophan |
| Clopamide      | l-valine       | Zopiclone       |
| Mitoxantrone   | Pioglitazone   | Pidolic acid    |
| Etoposide      | Cefitubuten    | Cyacetaclide    |
| Bepridil       | Canrenone      | Thiacetazone    |
| Buspironone    | calcium gluconate | Tilorone dihydrochloride |
| Benzbromarone  | Chlordiazepoxide | Cloxyquin     |
| Ouabain        | Fluconazole    | Florfenicol     |
| Cefadroxil     | dichlorophen   | Butacaine       |
| Primaquine     | Aminobutyric acid | Benzetimide   |
| Melatonin      | Meclizine      | Dextemide       |
| Neostigmine    | pentolinium tartrate | Dextrophan |
| Niridazole     | podoflox       | Oxfendazole     |
| Ceforanide     | Cefdinir       | Clinafloxacinc HCl |
| Biperiden      | Trandolapril   | Nitroxoline     |
| Pentamidine isethionate | betamethasone valerate | Bitoscanate |
| Cefaclor       | acetrizoate sodium | Clopidol      |
| Tiaprofenic acid | lactitol      | Rifamycin sv    |
| Vancomycin     | Dantron        | DL-gamma-Amino-beta-hydroxybutyric Acid |
| Budesonide     | Mercaptamine   | Pergizaine      |
| imipenem       | Meclofenamate  | Sulpiride (+/-) |
| Felodipine     | chlorguanide   | Scopolamine N-butyl bromide |
| Psoralens for systemic use | Benazepril | Potassium antimonyl tartrate trihydrate |
| Metixene       | Valsartan      | Nadifloxacin    |
| Ilohexol       | Telithromycin  | Sulfamoxole     |
| Benperidol     | Lindane        | Carbadox        |
| Drug Name        | Drug Name          | Drug Name           |
|-----------------|--------------------|--------------------|
| Terconazole     | Escitalopram       | Fleroxacin         |
| Sisomicin       | Dipyrocetyl        | Tosufloxacin       |
| Nystatin        | Aspirin            | N-Desmethylclozapine |
| Triflusul       | Ioxapine succinate | Chloralose         |
| Mesoridazine    | Nitrofurazone      | Tracazolate        |
| Amiodarone      | Podofilox          | Dibenzepine        |
| Amphotericin B  | Avermectines       | 3-formyl Rifamycin |
| Vigabatrin      | Triethylenemelamine| Sulfachloropyridazine |
| Probenecid      | Efornithine hydrochloride | Oltipraz          |
| Propylthiouracil| Arsenic trioxide   | Betamipron         |
| Trimethadione   | Samarium(III) acetate hydrate | Thioestrepton    |
| Lovastatin      | Exemestane         | Tetrachloroethylene |
| Tenoxicam       | Anthranilic acid   | Bromoform          |
| Phenindione     | Quinine            | Nonivamide         |
| Thiocolchicoside| Creosote, Beechwood Tar | Tetrandrine (s,s +) |
| Bisacodyl       | Cetalkonium chloride | cis(Z)-Flupenthixol dihydrochloride |
| ergocalciferol  | Mitomycin          | Sarafloxacin HCl   |
| Fluoxetine      | 6-Mercaptopurine monohydrate | Artemesin         |
| Selegiline      | Phenanthrene       | Ricobendazole      |
| Pyrazinamide    | Asparaginase       | Enrofloxicin       |
| Rifampicin      | Diethylstilbesterol| Benznidazole       |
| Ethionamide     | Gemcitabine        | p-Arsanilic acid   |
| Piracetam       | Silver (I) sulfadiazine, 98% | Methylphedrine    |
| Chloroquine     | Nithiamide         | Cinchophen         |
| Trimetazidine   | Thiabendazole      | N-Acetyl-L-leucine |
| Calcifediol     | d-Cycloserine      | Ritanserin         |
| Cisapride       | Paroxetine         | Acedoben           |
| Ciclopirox      | Hydroxyurea        | Idebenone          |
| Omeprazole      | Temozolomide       | Tribromoethanol    |
| Tiabendazole    | Lomustine          | Meclofenoxate      |
| Methoxamine     | Efornithine        | Lactitol monohydrate |
| Atenolol        | Metirosine         | Pyridoxal-5-phosphate |
| Molsidomine     | Nifuroxime         | Rebamipide         |
| Gliclazide      | Carvacrol          | Anethole-trithione |
| Ilobenguane     | Thymol             | Sodium butyrate    |
| Carbimazole     | Amodiaquin         | Nedaplatin         |
| mestanolone     | Androstanolone     | Pyrithioxin        |
| Hexetidine      | Histamine          | Ethenzamide        |
| Cetirizine          | Anthracene          | Cinromide          |
|---------------------|---------------------|-------------------|
| Atovaquone          | Quinaldine blue     | Azulene           |
| levamisole          | Capecitabine        | Cerium oxalate    |
| prasterone          | Dithiazanine iodide | Tioxolone         |
| Dirithromycin       | Bismuth tribromophenate | Cyclazocine  |
| Ceftazidime         | Chlorquinidal       | Octabenzone       |
| ethamivan           | Potassium permanganate | Aminothiazole  |
| Pilocarpine         | Quinine urea hydrochloride | Chromocarb      |
| Dicloxacillin       | (+)-p-Aminoglutethimide | Epirizole       |
| Cefotiam            | Cisplatin           | Acenpromazine     |
| Phenacetin          | Cytarabine          | Rolipram          |
| Tobramycin          | Thiourea            | Apocodeine        |
| Nifuroxazide        | Gallium (III) nitrate hydrate | Uracil      |
| Mycophenolic acid   | Acriflavine hydrochloride | Isrogladine maleate |
| Dosulepin           | Tartaric acid L-(-) | Isopaglumic acid  |
| Propafenone         | Iodoform            | Telenzepine       |
| Cyclizine           | Quinine hydrobromide | Metoclopramide   |
| Menadione           | Abacavir            | Procodazole       |
| Dinoprost           | Carmustine          | Dextrophan tartrate |
| Nitrofurural        | Strontium chloride hexahydrate | Fosfosal     |
| Betahistine         | Epirubicin          | Fampridine        |
| Tolazamide          | Bicalutamide (Casodex) | Aceneuramic acid |
| Colistin            | Melphalan           | Monophosphothiamine |
| Daunorubicin        | Roxarsone           | L-Ornithine       |
| Artemisinin         | Carbon Tetrachloride | Adenosine triphosphate disodium |
| Bromperidol         | Methenamine mandelate | Pyridoxamine, Dihydrochloride       |
| Sulfasalazine       | Pentamidine         | Oxeladin citrate salt |
| Prenylamine         | Naphthalene         | Cycloheximide     |
| dipivefrine         | Gold(III) chloride trihydrate | Trimebutine  |
| Vitamin B2 (Riboflavin) | Amifostine         | Fomocaine         |
| Folic acid          | Irinotecan hydrochloride trihydrate | Dimethadione   |
| Dydrogesterone      | Fumagillone         | Tricaprilin       |
| Mepenzolate         | Saponin, from quillaja bark | Storax     |
| Flurandrenolide     | Isoniazid           | D-glucosamine sulfate |
| Finasteride         | Chloramine-T hydrate | Roxatidine acetate HCl |
| Cefmetazole         | Quinine bisulfate   | Flavin adenine dinucleotide  |
| Phenazopyridine     | Dichlorophene       | Benzyl nicotinate  |
| Tubocurarine        | Fenticlor           | Carbaryl          |
| Noscapine         | Mitotane          | Clothiapine       |
|------------------|-------------------|-------------------|
| Atropine         | Cladribine        | Pyrogallol        |
| rescinnamine     | Anastrozole       | Roxindole Mesylate|
| trihexyphenidyl  | Mechlorethamine HCL | Etofylline      |
| Promazine        | Toremifene        | Aceglutamide      |
| Halcinonide      | 4-Hexylresorcinol | Sodium feredetate |
| Suxibuzone       | Silver nitrate    | Lipoic acid, alpha|
| Cefuroxime       | Acetarsone        | Butetamate        |
| Sulfapyridine    | Echinacea juice   | Phenylpropanol    |
| tetracaine       | p-Aminosalicylic acid | Carbocysteine |
| Papaverine       | BERBERINE         | Eserine           |
| atropine         | Lamivudine        | Imipraminoxide    |
| galantamine      | Cefepime hydrochloride | Lithium Hydroxide |
| Picrotoxin       | Voriconazole      | Hydroxyquinone    |
| sulpyrine        | Calcium propionate| D-Glucosamine 2-sulfate|
| Lanatoside C     | Cefpodoxime proxeit | Mecobalamin    |
| estropipate      | Ceftriaxone       | Ascorbic acid 6-palmitate |
| Terazosin        | Cephradine        | Tulobuterol       |
| Leflunomide      | Oxycloprosone     | Carbophenothion   |
| Vitamin B1 (Thiamine) | Triple dye     | Difluprednate    |
| Vitamin B6 (Pyridoxine) | Potash, sulfated | Bifemelane       |
| hydrocortamine hydroc | Sodium propionate | Ebselen          |
| Sparteine        | Didanosine (2',3'-dideoxyinosine) | Amylene hydrate |
| gelsemin         | Zinc undecylenate | Bismuth aluminate |
| citoilone        | Imiquimod         | Durapatite        |
| Ethotoin         | Doxycycline hyclate | Procateterol     |
| tetrahydrozoline nitrate | Fosomycin tromethamine | Pimagedine Aminoguanidine bicarbonate |
| Alclometasone    | Daptomycin        | Zinc carbonate    |
| Podophyllotoxin  | Sodium lauryl sulfate | Clobetasone butyrate |
| Dihydroergocristine | Aminacrine       | Mizoridine        |
| syrosingopine    | Domiphen bromide  | Decitabine        |
| Hydroquinine     | Anisomycin        | Diloxamide furoate|
| Diffloasone      | Nevirapine        | TNP-470           |
| Citalopram       | Benzoylpas calcium | Lisofylline      |
| Benfotiamine     | Oxiconazole nitrate | Monoethanolamine |
| clorcyclizine    | Phthalylsulfacetamide | Eucatropine     |
| benzetonium      | Mafenide          | Clofibric acid    |
| Clobetasol       | Mezlocillin sodium | Congo red         |
| Penicillin V | Triclosan | Bronopol |
|------------|-----------|----------|
| Mometasone | Carbazole  | Aluminum Phosphate |
| Dacarbazine | Oxamnique  | Puromycin |
| Demecarium | Nelfinavir mesylate | Silibinin |
| Emetine    | Triacetin  | Cianidanol |
| Succinylsulfathiazole | Rimantadine | Efaroxan |
| Sulfamerazine | Propionic acid sodium salt | Lomerizine HCl |
| pramocaine | Sulfadoxine | Chondroitin sulfate A |
| Fluorometholone | Penicillin G benzathine | Pentifylline |
| Naproxen   | Penicillin V | Polyoxyl 10 oleyl ether Brij 92 |
| Metoprolol | Tazobactam sodium salt | Carbamide peroxide |
| trihexyphenidyl | Ferric chloride anhydrous | Bemesetron |
| yohimbin | Streptomycin sulfate | Formestane |
| Racecadotril | Lopinavir/Ritonavir | Gold sodium thiocyanate |
| quinisocain | Efavirenz | Oxolamine |
| Benzocaine | Itraconazole | Nitrocefin |
| Bromopride | Valacyclovir | Adrenaline hydrochloride |
| mestanolone | Cefprozil | Thyropropic acid |
| trioxsalen | Furaltedone | Anazolene sodium |
| Streptozocin | Sulfabenzamide | Debrisoquin sulfate |
| Medrysone | 5-Chlorosalicylanilide | Denopamine |
| Ajmaline | Potassium chlorate | Bithionoloxide |
| Diclofenac | Cinchonine sulfate | Dicarboxylic acid |
| vincamine | Terbinafine | Tegafur (Ftorafur) |
| Glimepiride | Penciclovir | Mitotane |
| Flunisolide | Cinnamyl salicylate | Aspartame |
| Isosorbide dinitrate | Potassium iodide | Pantethine (D-Pantethine) |
| Diphenylpyraline | Linezolid | Benzaldehyde |
| cephalothin | Sparfloxacin | Cabufacon |
| Sulfamethizole | 4-Nitrophenol | Norfenefrine |
| Demeclocycline | Captan | Abamectin |
| Meclofenoxate | Sodium perborate tetrahydrate | Bumetazone |
| Flecaainide | Meglumine | Broxuridone |
| Glycopyrrolate | Tioconazole | Secnidazole |
| guanadrel sulfate | Undecylenic acid | Ditiocarb |
| Sulfanilamide | Cefonicid sodium | Potassium canrenoate |
| Isopropamide | Cefpiramid | 1-Pentanol |
| Iopamidol | Ceftizoxime | 4-Aminobutyric acid |
| Iopromide          | Sulbactam                          | Bopindolol Maleate        |
|--------------------|------------------------------------|---------------------------|
| Theophylline       | Bromthymol blue, sodium salt       | Althiazide                |
| Piromidic acid     | Ethyl vanillate                    | Bisoctrizole              |
| Norgestrel and estrogen | Veratrole                        | Carglumic acid            |
| Spiramycin         | Amantadine                         | Itopride HCl              |
| Diethylstilbestrol | Azithromycin dihydrate             | Oxaceprol                 |
| merbromin          | Cefmenoxime hydrochloride          | Aurothioglucose           |
| levonordeprin      | Carbomycin                          | Oxiniacic acid            |
| Cinoxacin          | Penicillin V potassium             | Citrate-Dextrose solution |
| Methazolamide      | Penicillin G                        | Hydrastinine              |
| Pyrithyldione      | Sulfisomidine                       | Lorglumide                |
| Spectinomycin      | Dodecylbenzenesulfonic acid, sodium salt, tech | Meglutol |
| Trichlormethiazide | Paraformaldehyde                   | Broquinaldol              |
| Cloperastine       | Ammonium citrate                   | Dizocilpine               |
| Piperacillin       | Castile soap                        | I-methionine              |
| Tinidazole         | Zinc sulfate                        | Clodronate disodium       |
| Sulfadimethoxine   | Isopropyl alcohol                  | Mitobronitol              |
| isoetharine        | Methylbenzethonium chloride         | Barmethan sulfate         |
| Amrinone           | Ketamine/Xylazine                  | Pravastatin lactone       |
| Cromoglicic acid   | Cisatracurium besylate             | Bismuth Sodium Triglycollamate |
| Bucladesine        | Isobutamben (Isobutyl 4-amino benz oate) | Tenatoprazole        |
| Cefsulodin         | Ethyl vinyl ether                  | L-Galactose               |
| beclomethasone     | Methotrimetazine                   | Desmethylastemizole       |
| Sulfamethoxypyridazine | Regular human insulin injection | Fiduxosin |
| sulfamethazine     | Potassium iodate                   | Lobeline (-) Hydrochloride |
| Guaifenesin        | 2,4-Dinitroanisole                 | Melengestrol acetate      |
| Leucovorin         | Proflavine hemisulfate salt hydrate, powder | Dimethicone |
| methacholine chloride | Sodium hypochlorite solution        | Indigotindisulfonate      |
| Carboxinomine      | Scopolamine (-)                    | Allythioure    |
| Clidinium          | Tramadol hydrochloride             | Pempidine                |
| sulfamonomethoxine | Dipyrone                           | Phosphocreatine           |
| benzthiazide       | Anisotropine methylbromide         | Bipenamol                |
| Simvastatin        | Mivacurium chloride                | Acadesine                |
| Fenoprofen         | Quinestrol                         | Acetomenaphthone          |
| dicumarol          | Terpene resin                      | Bendazol                 |
| Methimazole        | Ammonium sulfate                   | Brivudine                |
| Ribostamycin       | Tetraethylammonium chloride hydrate | Cirazoline hydrochloride |
| Drug                         | Drug                         | Drug                         |
|------------------------------|------------------------------|------------------------------|
| sulfameter                   | Thymol iodide                | Amperozide                   |
| bergenin                     | Tizanadine                   | Imazodan                     |
| Cefoxitin                    | Chlorobutanol                | Ergothionineine              |
| Ifosfamide                   | Chloroform                   | Bilirubin                    |
| novobiocin sodium            | Decamethonium Bromide        | RIAA 94                      |
| Reserpine                    | Diphenoxylate hydrochloride/Atropine sulfate | Conduritol |
| Fluocinonide                 | Norgestrel                   | Kavain                       |
| Isoacarboxazid               | Zinc peroxide                | Bretazenil                   |
| azelaic acid                 | Iodine 0.1 mo ICl/I          | Butaclamol hydrochloride (+) |
| Vidarabine                   | 2-Phenoxyethanol             | Enprofylline                 |
| Zomepirac                    | 3,5-Dibromosalicylaldehyde   | Bromofos                     |
| Azlocillin                   | Risocaine                    | Alfafosfalin                 |
| triamterine tartrate         | L-Hydrocystine hydrochloride | Naphthol blue black          |
| Nafcillin                    | Chloroprocaine               | Phytic acid, dodecasodium salt hydrate |
| Procyclidine                 | Phenacaine                   | Tartrazine                   |
| Trimipramine                 | Migtitol                     | Ginkgoalide A                |
| Bendroflumethiazide          | Sodium perchlorate monohydrate | Shikimic acid               |
| Mephenentermine              | Ammonium phosphate dibasic   | Butacetin                    |
| Cefamandole                  | Povidone iodine              | Cilostamide                  |
| Hexylcaine                   | Thonzonium bromide           | Furafylline                  |
| Pridinol                     | Brilliant green              | Butylated hydroxytoluene     |
| paroxetine hydrochloride     | Ammonium salicylate          | Antimony (III) sulfide       |
| Doxycycline                  | Valethamate bromide          | Zimelidine dihydrochloride   |
| Lithothronine sodium         | Aminopentamide sulfate       | Tanshinone IIA               |
| Roxithromycin                | Diperodon hydrochloride      | Nifekalant                   |
| Suprofen                     | Insulin lispro               | Vitamin E nicotinate         |
| Deferoxamine                 | Human insulin                | S(+) - Terguride             |
| Cefazolin                    | Cetyl alcohol (1-Hexadecanol) | Carsalal                     |
| Chlorotrianisene             | 2-Iodobenzoic acid           | Fumaranol                    |
| Dienestrol                   | 2-Phenylphenol               | Adrafolin                    |
| Pipenzolate                  | Dichlorodiphenyl-methane     | Etazolate Hydrochloride      |
| Gabapentin                   | Salicylic acid               | Denbufylline                 |
| Raloxifene                   | Camphor                      | Eseroline                    |
| Etidronic acid               | Rocuronium bromide           | Metrifudil                   |
| Theoebromine                 | Benactyzine HCL              | Genistein                    |
| Indoprofen                   | Sodium fluoride              | Quinpirole dihydrochloride   |
| mestranol                    | β-Estradiol                  | Epicatechin (-)              |
| Paromomycin                  | Potassium perchlorate        | Docebenone                   |
| Ioversol          | Benzoin                          | A-Cypermethrin  |
|-------------------|----------------------------------|----------------|
| Sulconazole       | Bornyl acetate, (-)-             | Benzaron        |
| Gadopentetic acid | 5 Aminosalicylic acid            | Androstenedione |
| Diloxanide        | Benoxinate                       | Eticlopride hydrochloride (S) |
| Flucytosine       | Trolamine                        | Phlorizin       |
| Nitrendipine      | Ethoxazene                       | Spiroxtarine    |
| desoxycortone     | Oxyphenonium bromide             | Ursolic acid    |
| Bacitracin        | Protirelin                       | Coumestrol      |
| Tolmetin          | Human insulin                    | Pentetic acid   |
| Scopolamine       | Terpineol mixed isomers          | Aconiazide      |
| diclofenamide     | Cetylpyridinium bromide monohydrate | Bentonite     |
| Aminophylline     | Chlorothymol                     | Bromocyclen     |
| crotamiton        | Phenyl salicylate                | Bioallethrin    |
| Xamoterol         | Salicyl alcohol                  | Indatraline hydrochloride |
| Phenoxybenzamine  | Butamben                         | Sulfoisalicylic acid |
| Bephenium         | Eugenol                          | 2-Iodomelatonin |
| Promethazine      | Vecuronium bromide               | Nisoxetine hydrochloride |
| Ketorolac         | Megestrol Acetate                | Harmine         |
| Azacitidine       | Cabergoline                      | Alpha bisabolol |
| Furazolidone      | 17β-Estradiol Dipropionate       | Amaranth        |
| moxalactam disodium | Estrone                       | Bromebric acid  |
| ethopropazine     | Chlorphenoxamine hydrochloride   | Butylated hydroxyanisole |
| Bemegride         | Clemizole                        | Bromophenol Blue, sodium salt |
| Primidone         | Octodrine                        | Pirfenidone     |
| Tyloxapol         | Dyphylline                       | Pregnenolone    |
| Altretamine       | Epinastine hydrochloride         | Brilliant Blue  |
| Ethynodiol Diacetate | Pholedrine                   | Quinelorane dihydrochloride |
| iodipamide meglumine | Sodium nitroprusside            | α-Ketoglutaric acid |
| Chloropyramine    | Strophanthin K                   | Epicatechin gallate (-) |
| Nadolol           | Troglitazone                     | Benmoxin        |
| Ganciclovir       | Chlormadinone acetate            | Butoxamine hydrochloride |
| Carbachol         | Tripelennamine                   | Aldosterone     |
| aesculin          | Hydromorphone polistirex/chlorpheniramine polistirex | Camylofine dihydrochloride |
| Pralidoxime       | Desloratadine                    | Zardaverine     |
| Aminohippuric acid| Norephedrine Hydrochloride       | Sodium stibogluconate |
| Megestrol         | Potassium guaiacolsulfonate      | Fluphenazine N-mustard |
| Nimodipine        | Vasopressin                      | 4-Hydroxydebrisoquin |
| Octopamine        | Enalaprilat                      | Decoycinine     |
| Propantheline | Isosorbide | Myristic acid |
|--------------|------------|---------------|
| Atenolol     | Etidronate disodium | Iocetamic acid |
| Urapidil     | Insulin glargine | Rolitetracycline |
| Pipemidic acid | Levalbuterol | nicotinic acid |
| Nilutamide   | Oxtiprylline | Albuterol |
| Proparacaine | Olopatadine hydrochloride | N,N-Dimethyhexylamine |
| Carbenoxolone | Azelastine HCl | Azatadine maleate |
| Iodixanol    | Amlodipine besylate | Phenyltoloxamine |
| Fluvastatin  | Hexamethonium Chloride | Lofexidine |
| Hymecromone  | Dextran | Nitroglycerine |
| bretylium tosylate | Alginic acid free acid | Eptifibatide |
| Meglumine antimonate | DESOXIMETASONE | benserazide hydrochloride |
| Salmeterol   | Pamidronate disodium | Ibuprofen |
Supplementary Table 3. Deletion of *tarO* in *S. aureus* RN4220, does not lead to sensitization to β-lactams. Fold change refers to the MIC of the antibiotic in the parent strain divided by MIC in the deletion strain.

| β-lactam Antibiotic | Fold change |
|----------------------|-------------|
| Ampicillin           | 1           |
| Cloxacillin          | 1           |
| Cefaclor             | 1           |
| Ceftizoxime          | 1           |
| Cefotaxime           | 1           |
| Cefoxitin            | 1           |
| Cefuroxime           | 1           |
| Piperacillin         | 1           |
**Supplementary Table 4.** Thienopyridine group of molecules in combination with cefuroxime against CA-MRSA USA300.

| Thienopyridine       | MIC thienopyridine (µg/mL) | FIC\(^1\) thienopyridine | MIC cefuroxime (µg/mL) | FIC\(^1\) cefuroxime | FIC Index\(^2\) |
|----------------------|-----------------------------|----------------------------|------------------------|------------------------|-----------------|
| Ticlopidine (Ticlid®) | > 128                       | 0.063                      | ≥ 256                  | 0.032                  | ≤0.063          |
| Clopidogrel (Plavix®) | > 128                       | 0.063                      | ≥ 256                  | 0.063                  | ≤0.125          |
| Prasugrel (Effient®)  | > 128                       | 0.25                       | ≥ 256                  | 0.250                  | ≤0.5            |

\(^1\) Fractional Inhibitory Concentration (FIC) = [X]/MIC\(_X\), where [X] is the lowest inhibitory concentration of drug in the presence of the co-drug.

\(^2\) FIC index = FIC\(_\text{thienopyridine}\) + FIC\(_\text{cefuroxime}\)

\[ a \quad b \quad c \]
**Supplementary Table 5.** Fold change in the MIC of various antibiotics, including several β-lactams, in the presence of ticlopidine against CA-MRSA USA 300.

| Antibiotic            | Fold change | High affinity binding to PBP2 (ref) |
|-----------------------|-------------|-------------------------------------|
| Chloramphenicol       | 1           | NA                                  |
| Clarithromycin        | 1           | NA                                  |
| Cycloserine           | 1           | NA                                  |
| Daptomycin            | 1           | NA                                  |
| Erythromycin          | 1           | NA                                  |
| Fosfomycin            | 4           | NA                                  |
| Kanamycin             | 1           | NA                                  |
| Levofloxacin          | 1           | NA                                  |
| Minocycline           | 1           | NA                                  |
| Neomycin              | 1           | NA                                  |
| Norfloxacin           | 1           | NA                                  |
| Novobiocin            | 1           | NA                                  |
| Streptomycin          | 1           | NA                                  |
| Trimethoprim          | 1           | NA                                  |
| Vancomycin            | 1           | NA                                  |
| Ampicillin            | 8           | ✓(7)                                |
| Cefaclor              | 16          | ✓(8)                                |
| Cefadroxil            | 1           | -                                   |
| Cefamandole           | 4           | -                                   |
| Cefotaxime            | 8           | ✓(7)                                |
| Cefoxitin             | 8           | -                                   |
| Cefsulodin            | 1           | -                                   |
| Ceftazidime           | 1           | -                                   |
| Ceftizoxime           | 16          | ✓(9)                                |
| Cefuroxime            | 64          | ✓(10)                               |
| Cephalixin            | 2           | -                                   |
| Cephalothin           | 8           | ✓(7)                                |
| Cephradine            | 2           | -                                   |
| Cloxacillin           | 8           | ✓(8)                                |
| Meropenem             | 2           | -                                   |
| Methicillin           | 4           | -                                   |
| Nafcillin             | 16          | ✓(8)                                |
| Oxacillin             | 16          | ✓(11)                               |
| Penicillin G          | 16          | ✓(7)                                |
| Piperacillin          | 8           | ✓(10)                               |

1Fold change refers to the MIC of the antibiotic alone divided by the lowest MIC of the antibiotic in combination.
**Supplementary Table 6.** FIC determination of cefoxitin in combination with β-lactams of high-affinity for PBP2 (*) and of low affinity for PBP2 against CA-MRSA USA300. Fold change represents the decrease in the MIC of the β-lactam in the presence of cefoxitin.

| Antibiotic      | Ref. for affinity | Fold Change | FIC Index |
|-----------------|-------------------|-------------|-----------|
| Cefuroxime *    | (10)              | > 64        | 0.039     |
| Ceftizoxime *   | (9)               | 128         | 0.094     |
| Oxacillin *     | (11)              | > 32        | 0.094     |
| Penicillin *    | (7)               | 32          | 0.094     |
| Ceftazidime     | (10)              | 8           | 0.250     |
| Cefsulodin      | (10)              | 2           | 1.00      |
| Cephradine      | (7)               | 4           | 0.750     |
Supplementary Table 7. Bacterial strains and plasmids used in this study.

| Strain         | Genotype/phenotype⁹                          | Ref. or source |
|----------------|---------------------------------------------|----------------|
| RN4220         | Restriction-deficient mutant                | (12)           |
| RN450          | Prophage-cured S. aureus strain 8325        | (13)           |
| EBI16          | SA178R1; RN4220 derivative, containing T7 pol | (2)            |
| EBI216         | SA178R1 tarO::spec (spec⁹)                  | (2)            |
| EBI214         | SA178R1 tarH::pSCH1382ΔtarH (erm)           | (2)            |
| Newman         | Clinical isolate (ATCC 25904)               | (14)           |
| HA-MRSA        | USA600, SCCmec type II                     | (15)           |
| HA-MRSA        | USA 100/800/NY, SCCmec type II             | (15)           |
| HA-MRSA        | SCCmec type III                             | (15)           |
| HA-MRSA        | USA 200/EMRSA16, SCCmec type II            | (15)           |
| HA-MRSA        | USA500, SCCmec type IV                     | (15)           |
| HA-MRSA        | SCCmec type III                             | (15)           |
| HA-MRSA        | USA400/MW2, SCCmec type IV                 | (15)           |
| HA-MRSA        | EMRSA15, SCCmec type IV                    | (15)           |
| CA-MRSA        | SCCmec type II                              | (15)           |
| CA-MRSA        | USA300, SCCmec type IV                     | (15)           |
| EBI230         | CA-MRSA USA300 tarO::spec (spec⁹)          | This study     |
| EBI228         | HA-MRSA EMRSA15 tarO::spec (spec⁹)         | This study     |
| EBI234         | HA-MRSA EMRSA15 tarO::spec pLI50-tagO (spec⁹, chl⁹) | This study |
|                | tarH::erm pCL55-tarH                       | This study     |

⁹ HA, hospital-associated isolate, CA, community-associated isolate

| Plasmid          | Description                                          | Ref. or source |
|------------------|------------------------------------------------------|----------------|
| pLI50            | E. coli / S. aureus shuttle vector (amp⁹, chl⁹)      | (16)           |
| pSweet-tagO      | Source for vector containing B. subtilis tagO (amp⁹, chl⁹) | (17)           |
| pLI50-tagO       | pLI50 with xylR-tagO from pSweet-tagO (amp⁹, chl⁹)   | This study     |
| pSweet-tarD      |                                                      | (18)           |
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