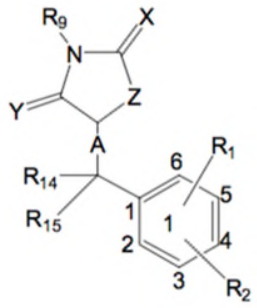
Claims

1. A composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by Formula I



Formula I

wherein X and Y are independently O, S, or NR_{10};

wherein Z is O, S, $CR_{11}R_{12}$, or NR_{13};

wherein R_1, R_2, R_9, R_{10}, R_{11}, R_{12}, R_{13}, [~~R_{14},~~]and R_{15}, are independently absent, hydrogen, $-C(O)R_{18}$, $-C(W)NR_{19}R_{20}$, or substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aroxy, arylalkyl, heteroalkyl, alkylaryl, halogen, alkylheteroaryl, $-NR_{16}R_{17}$;

wherein R14 is independently absent, $-C(W)NR_{19}R_{20}$, or substituted or unsubstituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, aroxy, arylalkyl, heteroalkyl, alkylaryl, halogen, alkylheteroaryl, $-NR_{16}R_{17}$;

wherein R_{16} and R_{17} are independently hydrogen, substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroalkyl, alkylaryl, or alkylheteroaryl;

wherein R_{18} is hydrogen, hydroxyl, or substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, aroxy, heteroaryl, arylalkyl, heteroalkyl, alkylaryl, or alkylheteroaryl;

wherein W is O, S, or NR_{21};

wherein R_{19}, R_{20}, and R_{21} are independently hydrogen or substituted or unsubstituted

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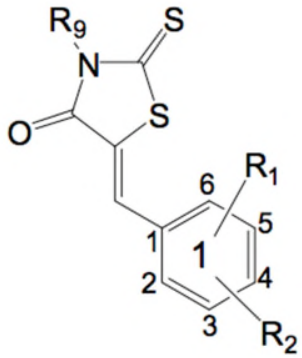
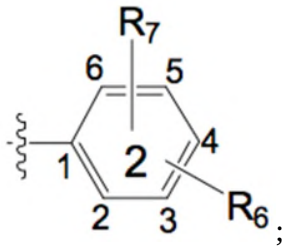
alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, cycloalkenyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroalkyl, alkylaryl, or alkylheteroaryl;
wherein A is a double bond or single bond; and
wherein R_{15} is absent when A is a double bond,
wherein the effective amount of the compound is effective to inhibit dihydrofolate reductase in a microorganism.

2. The composition of claim 1, wherein the compound is



Formula II wherein R_1 is -O-R4, -NR5R8, or -CH_2-R5; R_2 is halogen, absent, -O-CH_3, or -O-CH_2-CH_3; R_9 is –COOH, -CH_2-COOH, -CH_2-O-CH_3, or -CH_2-CH_2-O-CH_3; R_4 is -CH_2- R_5 or -CO-R_5; R_5 is



;

R_6 is a halogen or absent; and R_7 is halogen or absent.

3. The composition of claim 2, wherein R_1 is at a position selected from the group consisting of 2, 3, 4, 5, and 6; optionally, R_6 is at position 4; optionally, R_7 is at position 2 or 6 and optionally, R_2 is at position 3, 4, or 5.

4. The composition of claim 2 wherein the compound is

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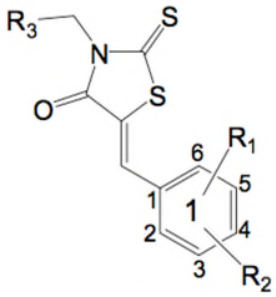
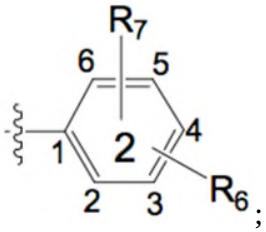


Formula IIA

wherein R_1 is -O-R_4, -NR_5R_8, or -CH_2-R_5; R_2 is halogen, absent, -O-CH_3, or -O- CH_2-CH_3; R_3 is -COOH or -CH_2-COOH; R_4 is -CH_2-R_5 or -CO-R_5; R_5 is

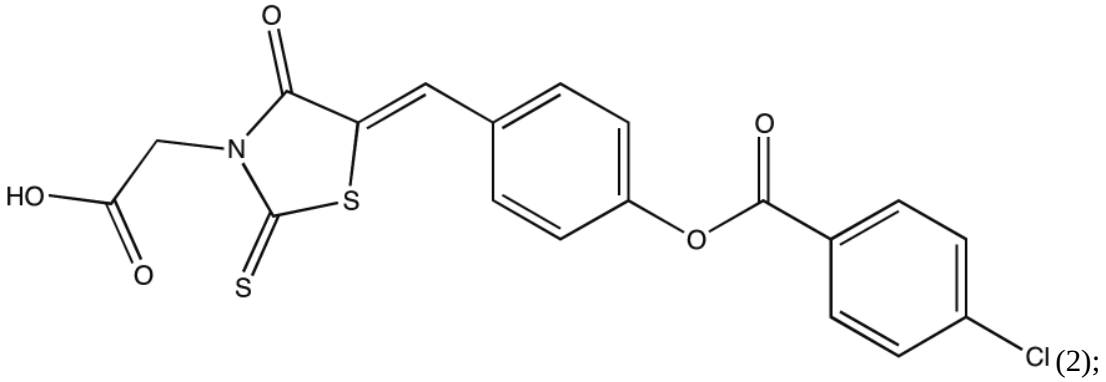


;

R_6 is halogen or absent; and R_7 is halogen or absent.

5. The composition of claim 4, wherein R_1 is at a position selected from the group consisting of 2, 3, 4, 5, and 6; optionally, R_6 is at position 4; optionally, R_7 is at position 2 or 6; and optionally, R_2 is at position 3, 4, or 5.

6. The composition of any one of claims 1-5, wherein the compound is selected from the group consisting of compounds of formulae 2-4, 6-7, 10, 13, 15, 17-20, 22, 24-25, 27-31, 34-37, 42, 44, 48-50, 52-53, 56, 60, 62-63, 69, 80-82, and 87:



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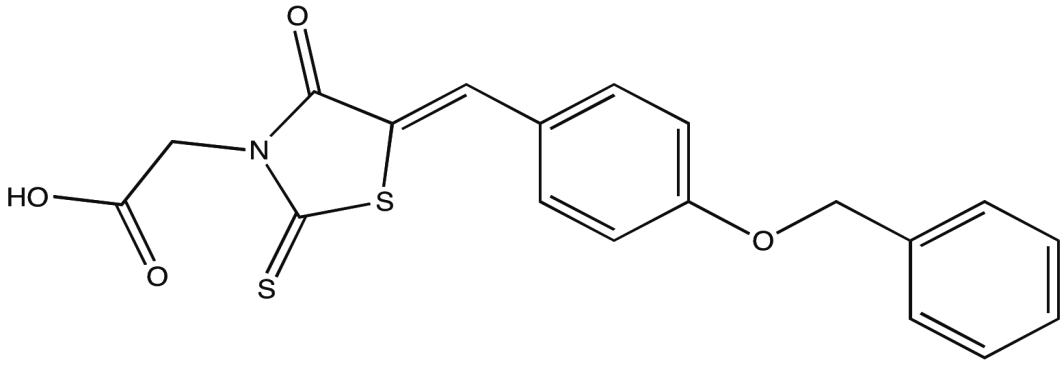

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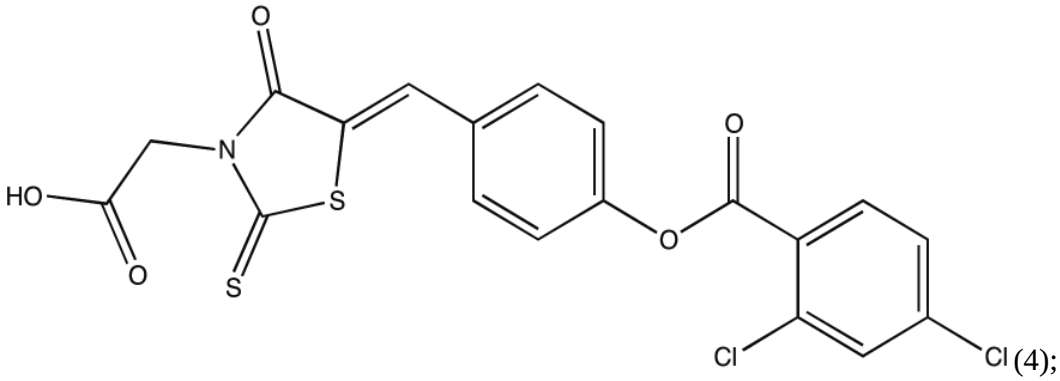

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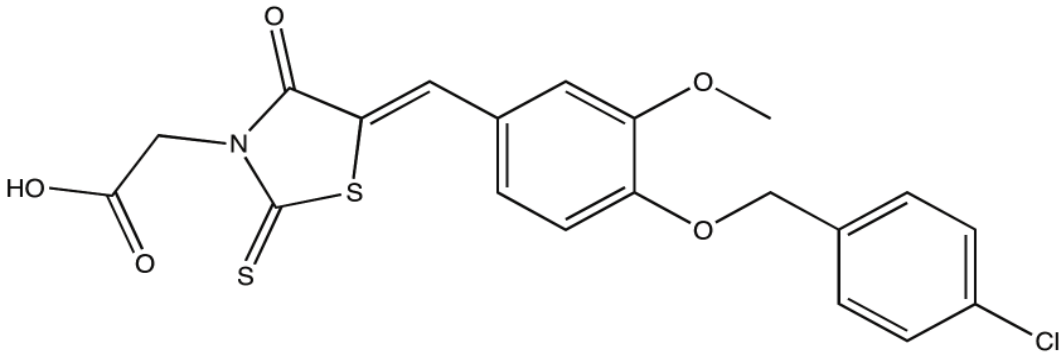

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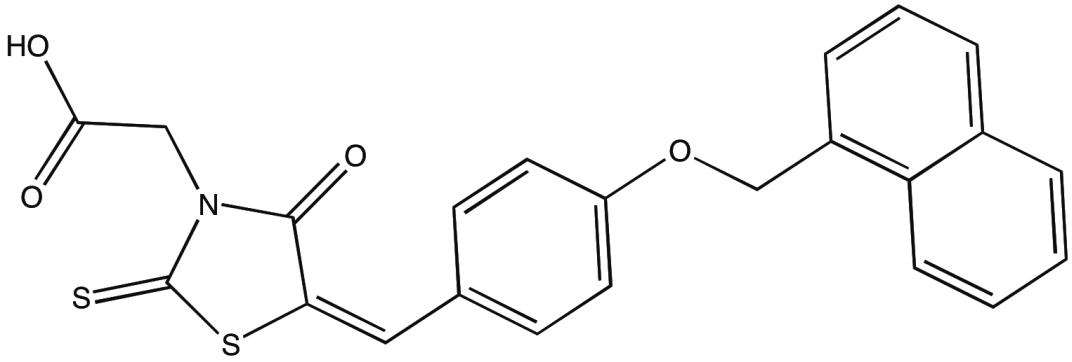

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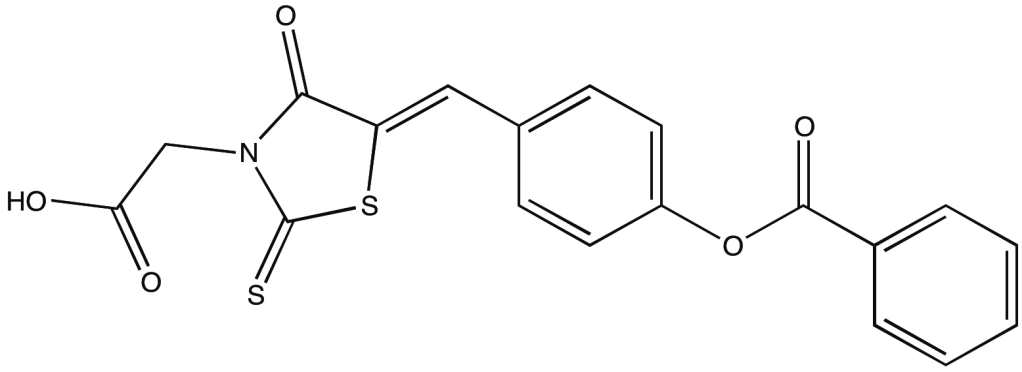

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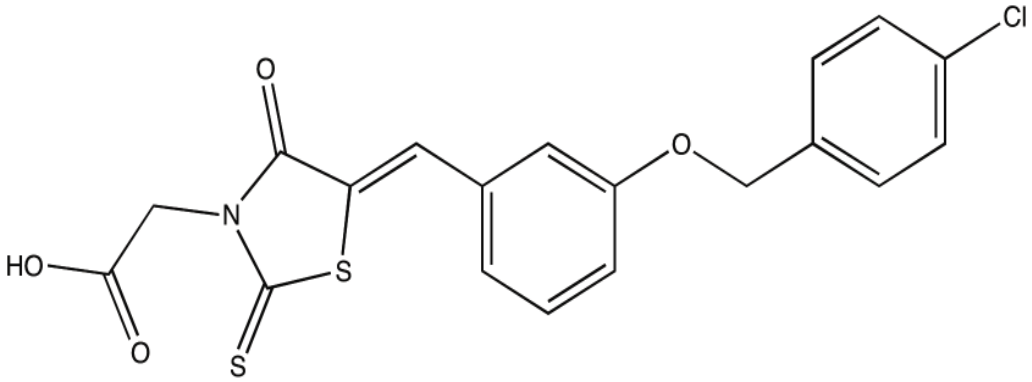

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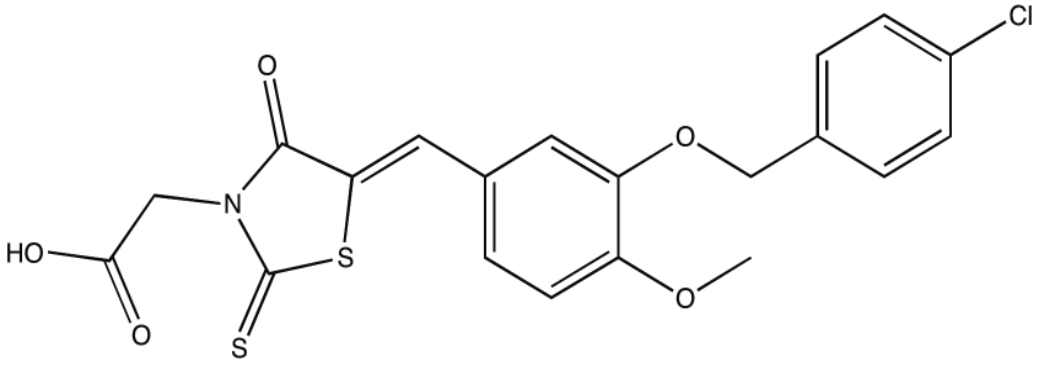

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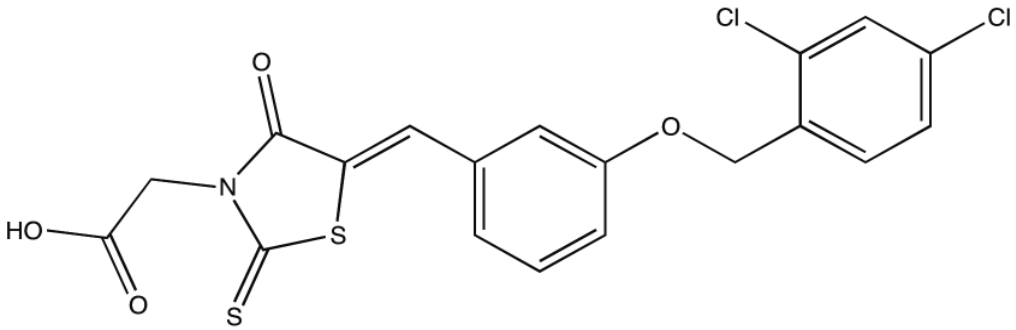

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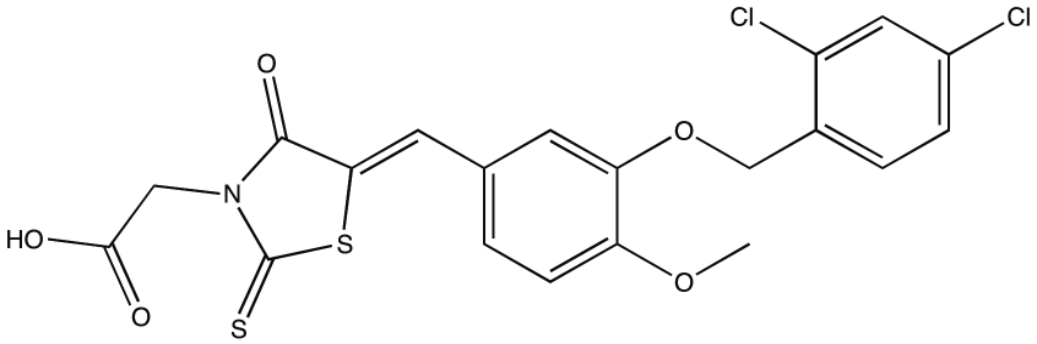

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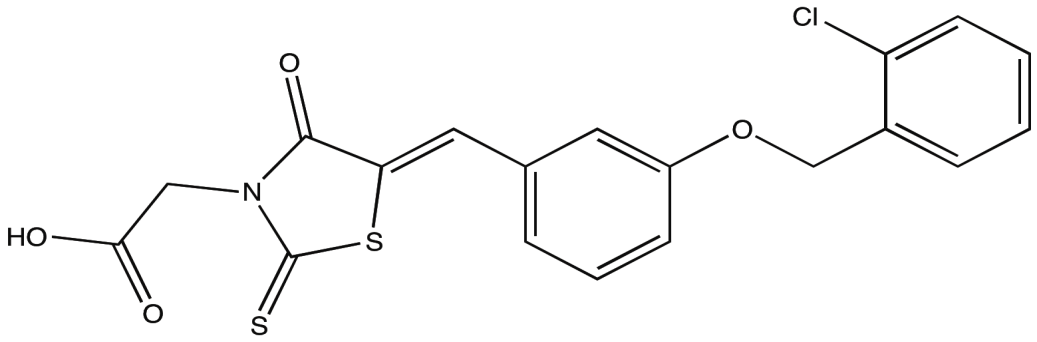

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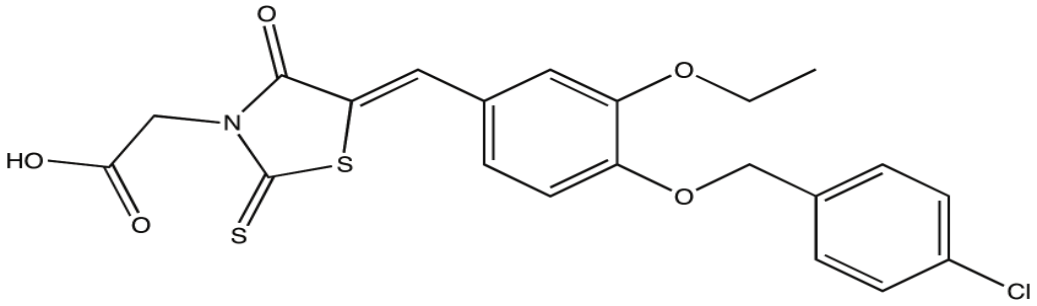

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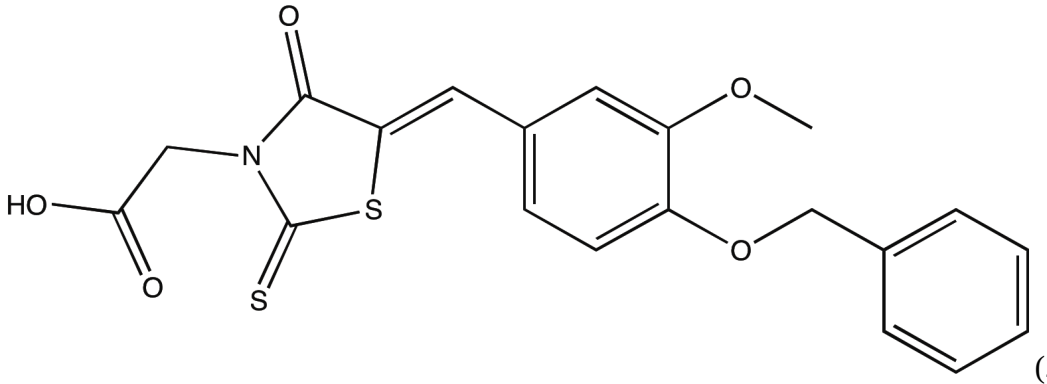

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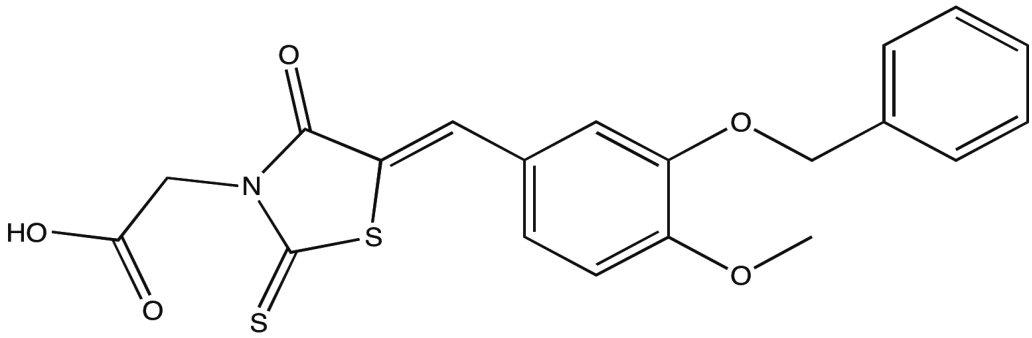

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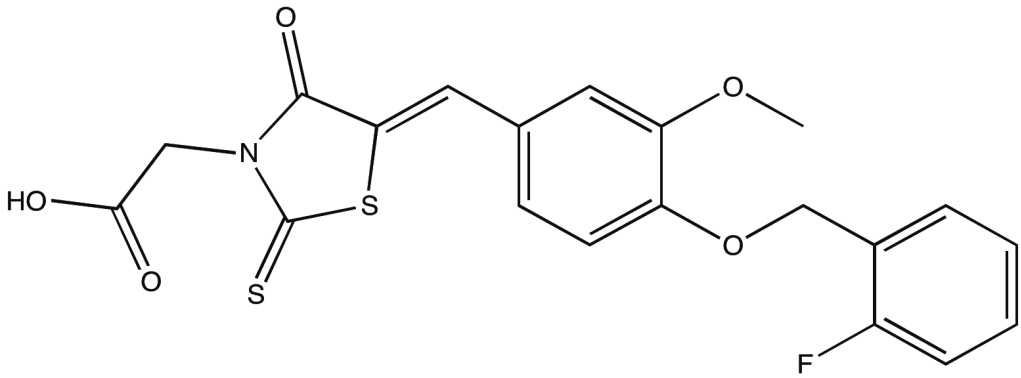

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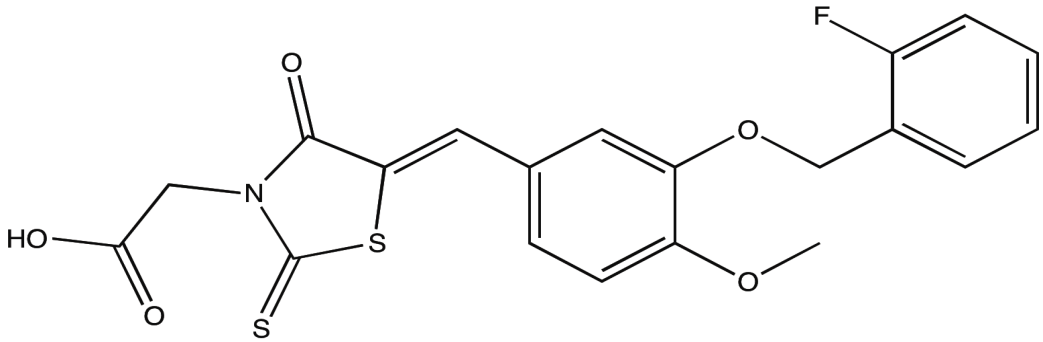

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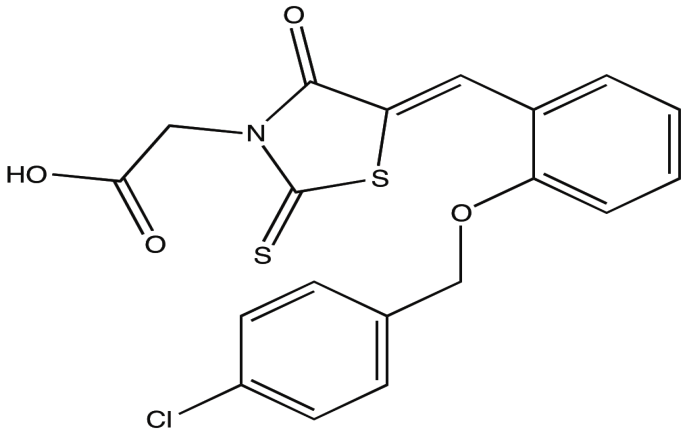

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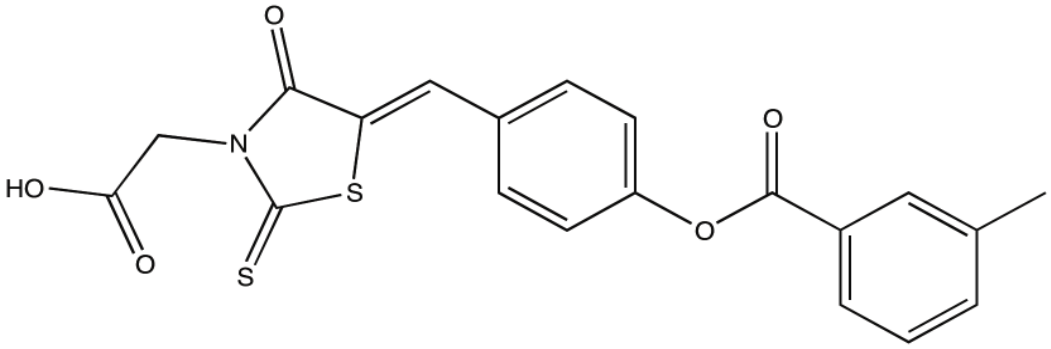

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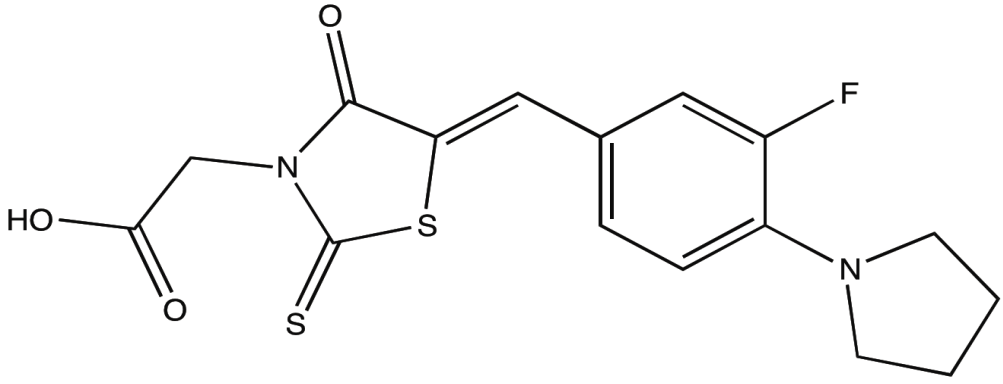

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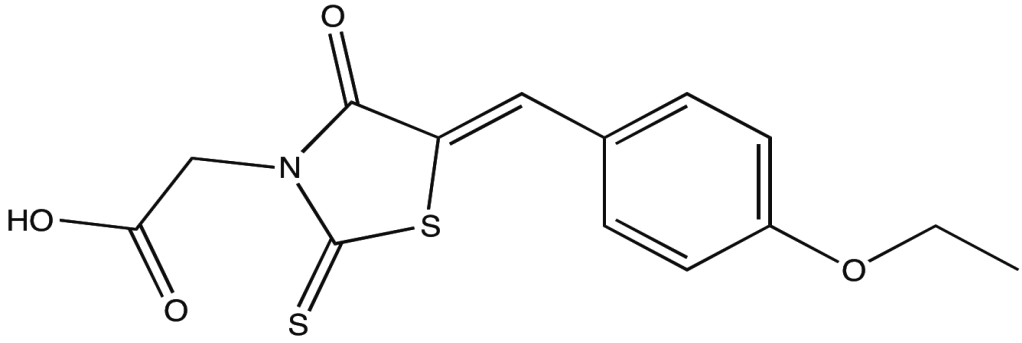

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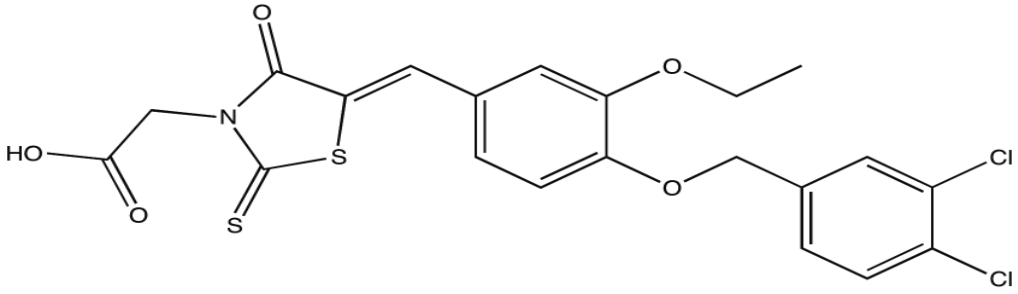

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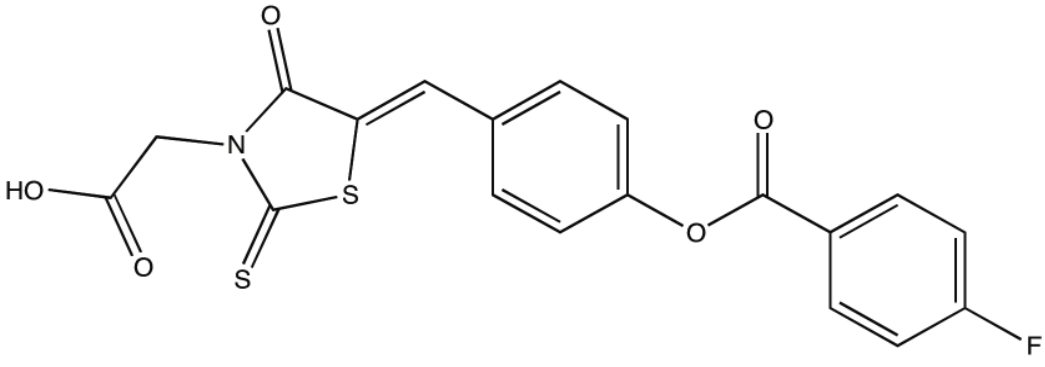

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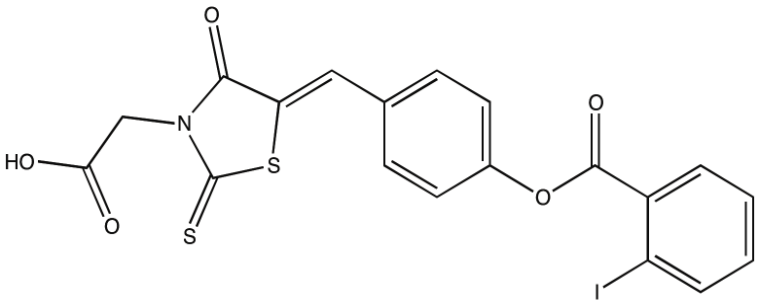

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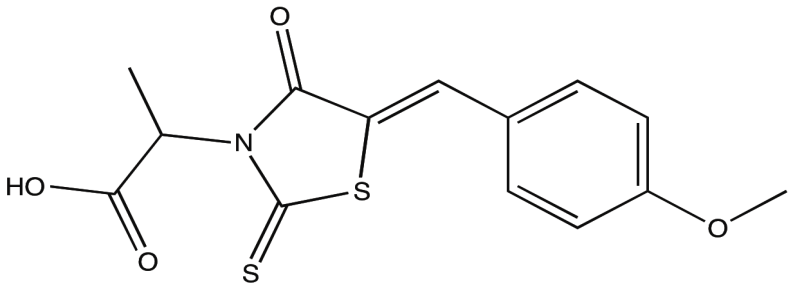

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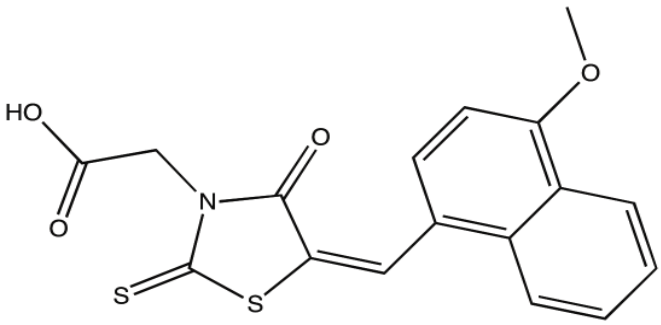

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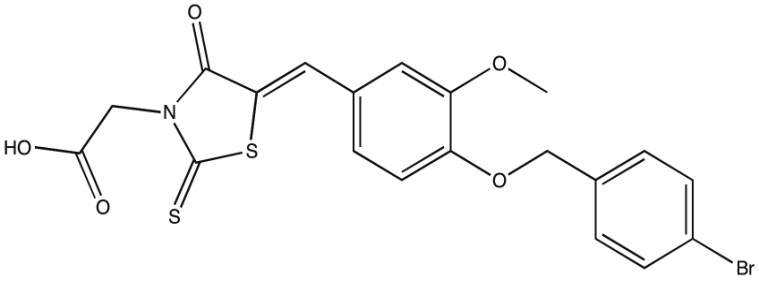

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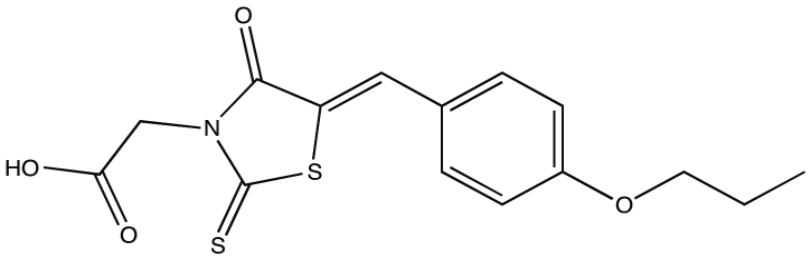

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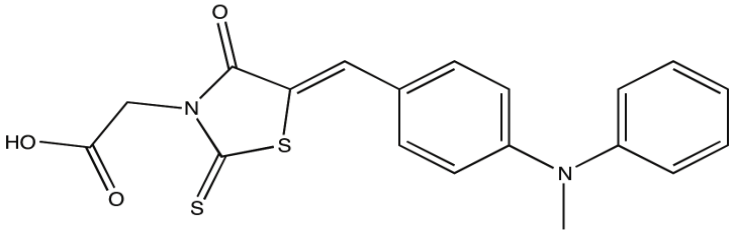

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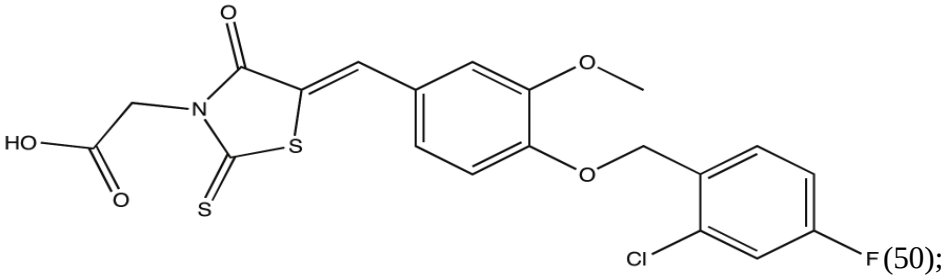

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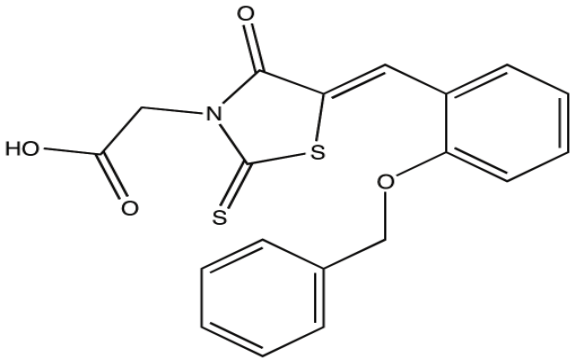

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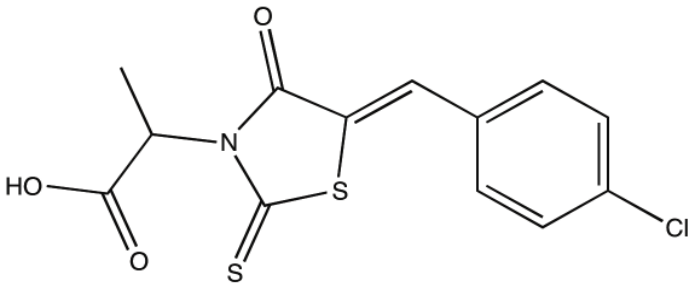

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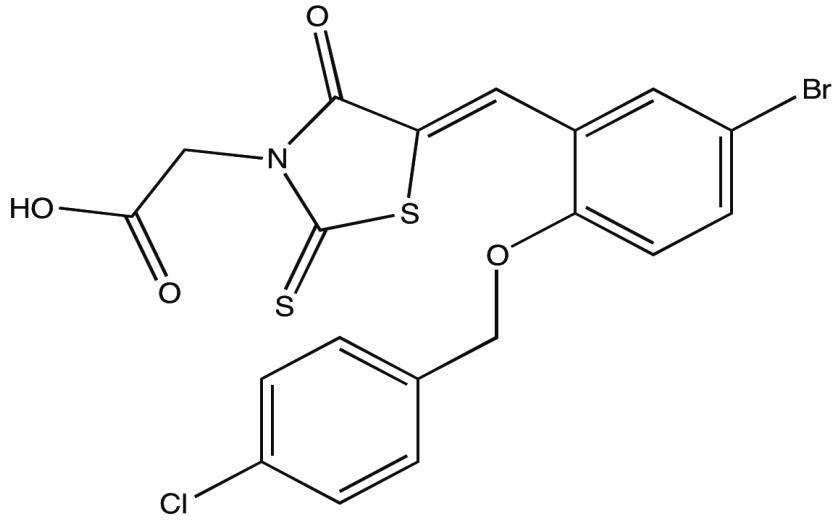

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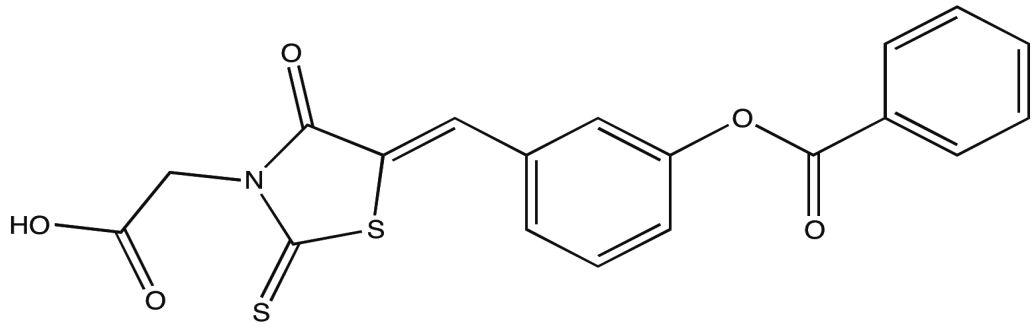

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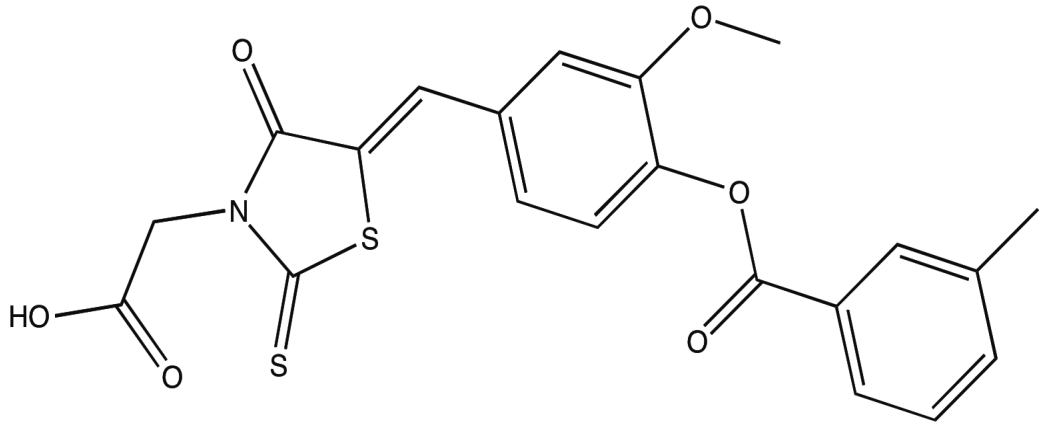

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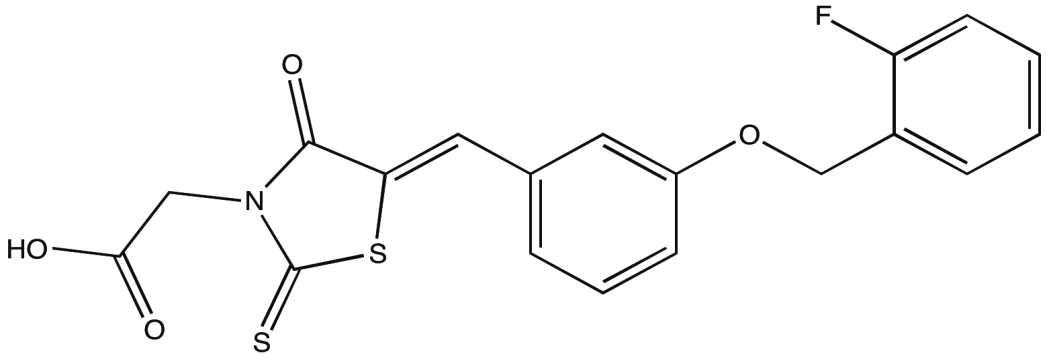

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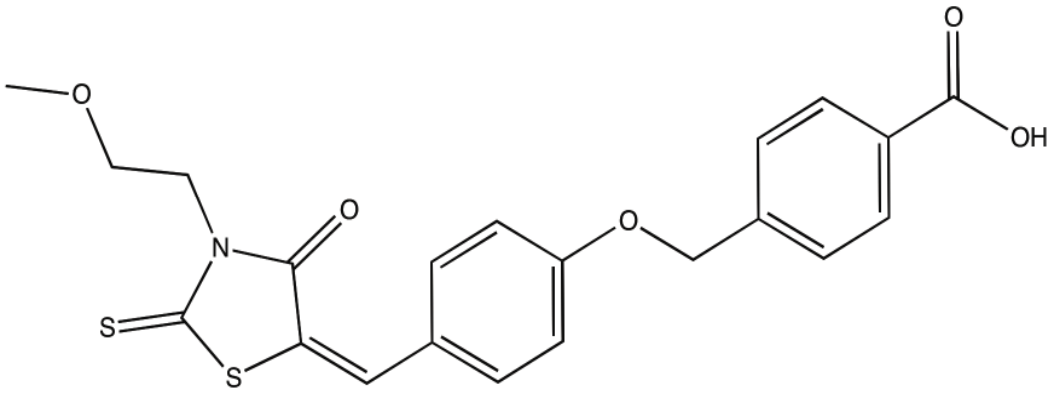

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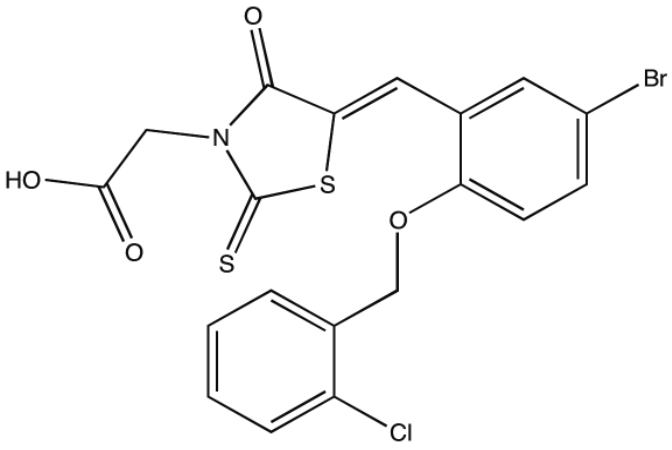

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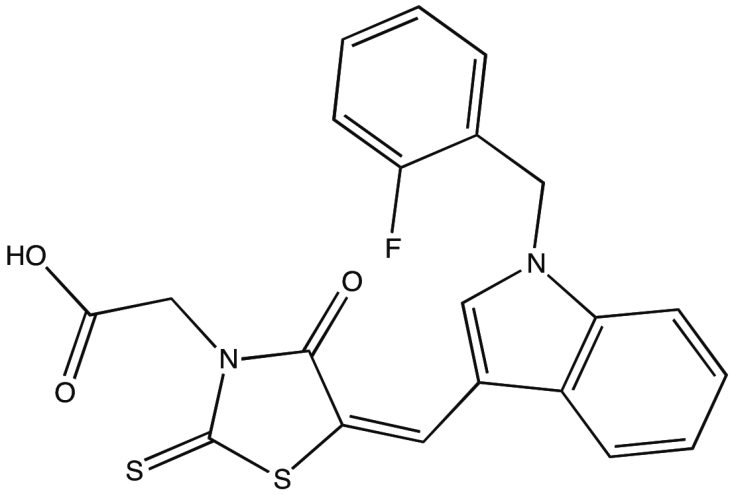

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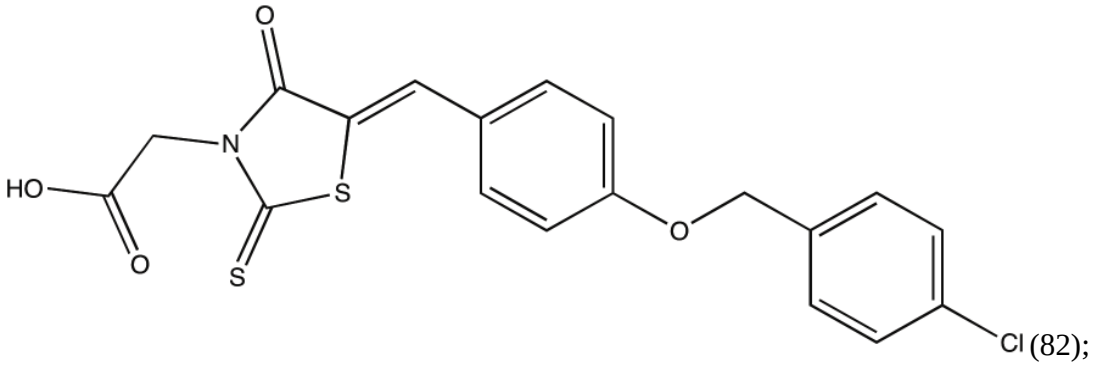

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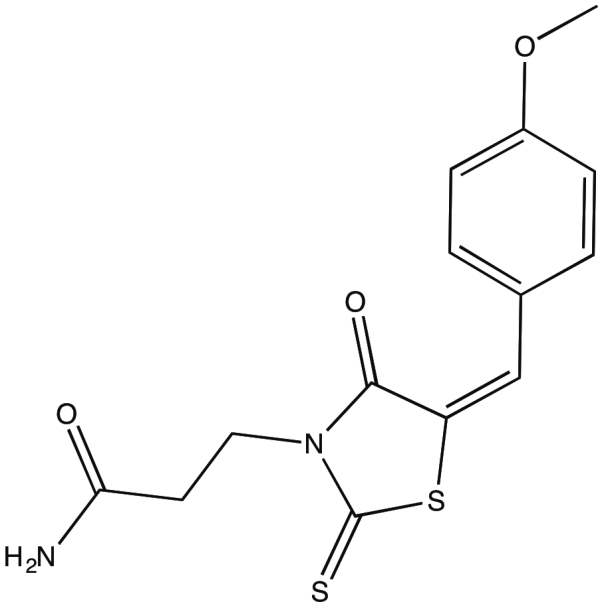

(87).

7. The composition of any one of claims 1-6, further comprising a therapeutically

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effective amount of an antibiotic.

8. The composition of claim 7, wherein the antibiotic is selected from the group consisting of gentamicin, amikacin, kanamycin, neomycin, spectinomycin, neamine and combinations thereof.

9. The composition of any of claims 7 or 8, wherein the therapeutically effective amount of the antibiotic is less than a therapeutically effective or therapeutically optimal dose of the antibiotic when administered to a subject in the absence of the composition.

10. Use of the composition of any one of claims 1-9 for treating a microbial infection in a subject, wherein the microbial infection is caused by one or more microorganisms.

11. The use of claim 10, wherein at least one of the microorganisms causing the infection is bacteria selected from the group consisting of methicillin-susceptible *Staphyloccous aureus, Pseudomonas aeruginosa, Listeria monocytogenes, Burkholderia cepacia, Escherichia coli, Enterococcus faecalis*, *Streptococcus pneumoniae*, or combinations thereof.

12. The use of claim 10 or 11, wherein the composition is administered parenterally or orally.

13. The use of any one of claims 10-12, wherein at least one of the microorganisms causing the infection is an antibiotic-resistant microorganism selected from the group consisting of a *Streptococcus pneumoniae, Campylobacter, Neisseria gonorrhoeae, Salmonella* (including drug-resistant non-typhoidal *Salmonella* and drug-resistant *Salmonella* serotype typhi), *Shigella,* Vancomycin-resistant *Enterococcus* (VRE), Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant Group A *Streptococcus,* Clindamycin-resistant Group B *Streptococcus*, Carbapenem-resistant *Enterobacteriaceae* (CRE), drug-resistant tuberculosis, Extended spectrum *Enterobacteriaceae* (ESBL), multidrug-resistant *Acinetobacter* (including MRAB),

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Clostridium difficile, Enteropathogenic E. coli (EPEC)*, Pseudomonas aeruginosa, H. pylori, Streptococcus anginosus* and *Uropathogenic E. coli* (UPEC).

14. The use of claim 13, wherein the microorganisms causing the infection is Methicillin-resistant *Staphylococcus aureus* (MRSA)

15. The use of claim 10 or 11, wherein the microorganism causing the infection is a multi-drug-resistant strain of *Listeria monocytogenes, Pseudomonas aeruginosa, Burkholderia cepacia, Enterococcus faecalis* and *Streptococcus pneumoniae*.

16. The use of any one of claims 10-15, wherein the infection is selected from the group consisting of impetigo, boils, abscesses, folliculitis, cellulitis, necrotizing fasciitis, pyomyositis, surgical/traumatic wound infection, and infected ulcers and burns), osteomyelitis, device-related osteoarticular infections, impetigo, secondarily infected skin lesions, meningitis, brain abscess, subdural empyema, spinal epidural abscess.

17. The use of any one of claims 10-16, wherein the infection is a urinary tract infection.

18. The use of any one of claims 10-17, wherein the subject is hospitalized or immunocompromised.

19. A method of disinfecting a surface in need thereof, the method comprising contacting the surface with the compound or composition of any one of claims 1-9.

20. The method of claim 19, wherein the compound is applied on the surface in the form of a spray, an aerosol, or a foam.

21. The method of claim 20, wherein the compound is imbibed into a cloth suitable for wiping down a surface to be disinfected.

22. The method of any one of claims 19-21, wherein the surface is the surface of an

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instrument selected from the group consisting of surgical instruments, cardiac and urinary catheters, implants, and ultrasound probes used in sterile body cavities.

23. The method of any one of claims 19-22, wherein the instrument is selected from the group consisting of endoscopes, laryngoscope blades, esophageal manometry probes, cystoscopes, anorectal manometry catheters, diaphragm fitting rings, gastroscopes, duodenoscopes, sigmoidoscopes, proctoscopes, colonoscopes, bronchoscopes, and laryngoscopes.

24. Use of the composition of any one of claims 1-9 for increasing the efficacy of an antibiotic when being co-administered to a subject in need thereof.

25. The use of claim 24, wherein the composition is co-administered separately, simultaneously, or sequentially with the antibiotic.

26. The use of claim 25, wherein efficacy of the antibiotic is increased by at least 2 fold measured as inhibition of growth of a microorganism in an in vitro assay in response to the antibiotic alone, compared to growth inhibition of the microorganism in response to a combination of the antibiotic and the composition.

27. Use of the composition of any one of claims 1-9 for reducing virulence of bacteria selected from the group consisting of methicillin-susceptible *Staphyloccous aureus, Pseudomonas aeruginosa, Listeria monocytogenes, Burkholderia cepacia, Escherichia coli, Enterococcus faecalis, Streptococcus pneumoniae* or combinations thereof in a subject.

28. The use of claim 27, wherein the compound is selected from the group consisting of compounds of formulae 3, 48, 49, and 87:

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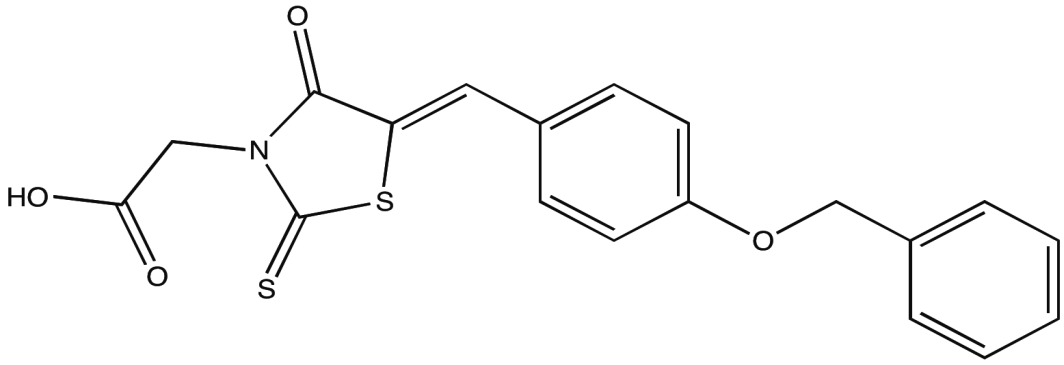
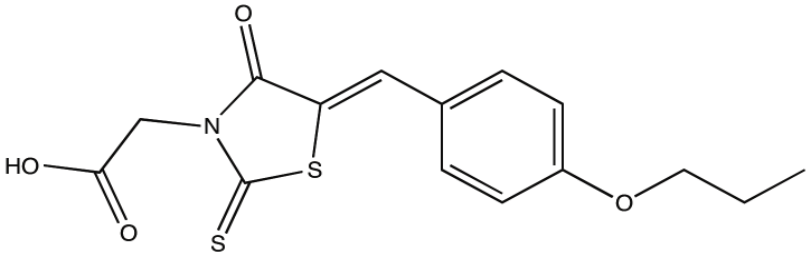
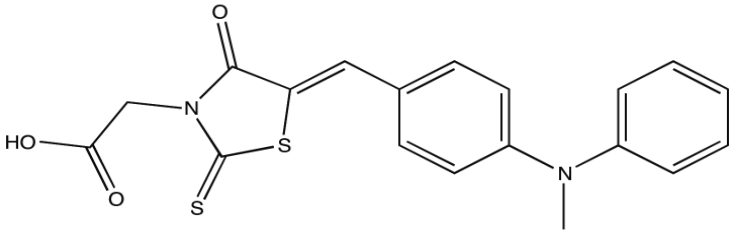


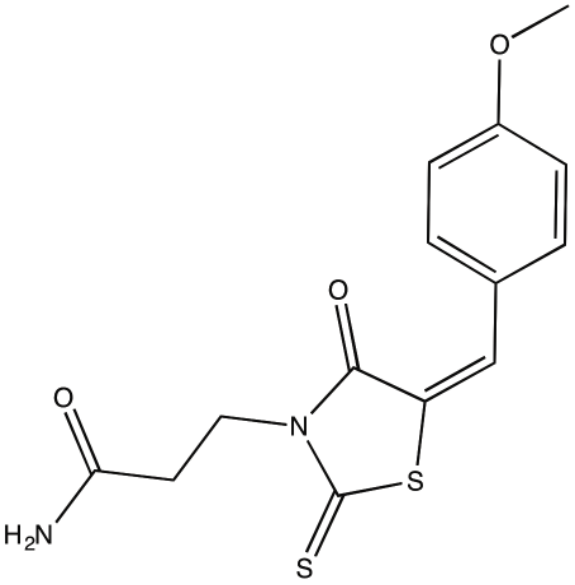
(3);



(48);



(49); and



(87).

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