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Synthesis and Evaluation of Some Novel 5-Arylidene-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) Thiazolidin-4-Ones as Anti-Microbial Agent

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Abstract: The development of combination chemotherapeutic drugs, each with distinct mechanisms and minimal side effects, is crucial in combating antimicrobial resistance. Discovering novel drugs with diverse mechanisms is laborious and time-consuming. Alternatively, combining multiple pharmacophores into a single molecule offers a promising strategy to develop more effective treatments. In this study, we synthesized and assessed the antimicrobial activity of novel 5-arylidene-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-ones.

Keywords: pyrimidine derivatives; antimicrobial agents; antibacterial; antifungal

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1. Introduction

Antibiotics have long served as humanity's primary weapon against pathogenic microorganisms [1–3]. However, microbes have resiliently developed novel survival strategies, leading to significant challenges. Decades after their discovery, it is humanity that has borne the brunt of this battle. We urgently require new drugs with mechanisms of action distinct from current antibiotics to effectively combat pathogenic microorganisms [2–6].

Development of successful novel antimicrobial agents targeting pathogens would decrease the demand of antibiotics and thereby lowering pressure that leads to antibiotic resistant mutations. Heterocyclic chemistry is one of most important branches of chemistry from the medicinal point of view [7,8]. Many heterocyclic compounds having hetero atoms like N, O and S showed biological activities which are important from pharmaceutical aspects. Drug resistant bacteria are becoming cause for the death of more than million people across the globe. Only in US, more than twenty-three thousand people die every year because of drug resistant pathogens. The current pace of drug development is inadequate to alleviate the global health threat of drug resistant organisms [9–13].

The pyrimidine moiety is a crucial heterocyclic compound widely present in the human body, exhibiting diverse biological activities such as antimicrobial, anti-inflammatory, anti-coagulant, antihypertensive, and antitubercular properties. It is integral to nucleic acids and enzymes in living organisms, offering potential as both antagonist and agonist drugs [14–16].

The rise of resistance to antibiotics and other antimicrobial agents poses a significant global challenge today [3,5,8]. As microbes develop resistance to current treatments, the battle between bacteria and humans intensifies, often resulting in adverse outcomes for human health. Addressing these challenges requires controlling the overuse of antibiotics,

which exacerbates resistance, and developing novel antibiotics with enhanced potency and efficacy [11–15].

To mitigate these challenges and improve treatment outcomes, discovering new antimicrobial agents with improved safety profiles remains paramount. This study focuses on the synthesis and evaluation of novel pyrimidine derivatives as potential antimicrobial agents, aiming to contribute to the ongoing efforts against microbial resistance [17–20].

2. Materials and Methods

For the determination of structures of newly synthesized compounds, we have used the sophisticated techniques like IR, ^{1}H NMR, ^{13}C NMR and Mass spectra. Aluminium coated TLC plates 60F254 (E. Merck) were used for reaction monitoring and checking the purity of all compounds. Ultraviolet (UV) light, or iodine vapour is used for visualization purpose. "Elemental analysis (% C, H, N) was carried out by Perkin- Elmer 2400 CHN analyser. IR spectra of all compounds have been taken on Perkin-Elmer FT-IR spectrophotometer in KBr. Mass spectrum was scanned on a Schimadzu LC-MS 2010 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker (400 MHz) and (100 MHz) spectrometer respectively, using DMSO-d_6 as a solvent and TMS as an internal standard". 1 Parts per million (ppm) is used as unit to express the chemical shifts.

Preparation of 7-chloroquinoline-6-carbaldehyde (I)

7-chloroquinoline-6-carbaldehyde **I** was prepared as per the method given in literature [21,22].

Preparation of 1-(7-chloroquinolin-6-yl)-N-(pyrimidin-2-yl)methanimine (II)

Compound **I** (0.01 mol) was dissolved in ethanol (95%) (20 mL) and pyrimidin-2-amine **A** (0.01 mol) was added to it. After adding CH_3COOH in catalytic amount, reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was then allowed to cool at room temperature and product formed as crystals was filtered [21–24]. The product was washed with cold ethanol (95%), dried and recrystallized from same solvent to obtain compound **II**.

Yield: 69%; m.p.: 163 °C; FTIR (cm^{-1}): 3462 (CH Streching), 1647 (C=O), 1541 (C=N), 846 (=CH), 659 (C-S); Anal. Calcd. for $C_{14}H_9ClN_4$: C-62.58, H-3.38, N-20.85; Found: C-62.67, H-3.29, N-20.77%.

Preparation of 2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl)thiazolidin-4-one (III)

Compound **II** (0.01 mol) was dissolved in 1,4-dioxane (20 mL) and thioglycolic acid (0.03 mol) was added to it. After adding $ZnCl_2$ in catalytic amount, reaction mixture was stirred at 110 °C for 5.5 h. The reaction mixture was then allowed to cool at room temperature and then poured into cooled dil.$NaHCO_3$ solution. Product obtained as dark cream colour was filtered and washed with same solution followed by cold methanol, dried and recrystallized from methanol to obtain compound **III**.

Yield: 59%; m.p.: 182 °C; FTIR (cm^{-1}): 3307 (CH Streching), 1602 (C=O), 1495 (C=N), 883 (=CH), 655 (CH), 584 (C-Cl); Anal. Calcd. for $C_{16}H_{11}ClN_4OS$: C-56.06, H-3.23, N-16.34; Found: C-56.13, H-3.15, N-16.27%.

Preparation of 5-arylidene-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-ones (IV)

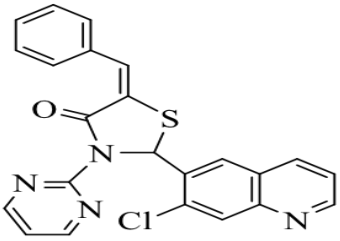
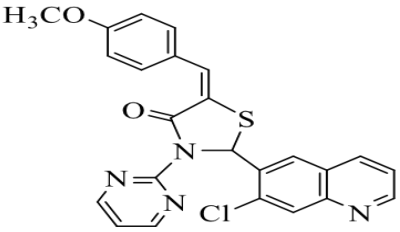
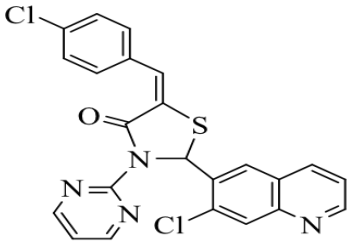
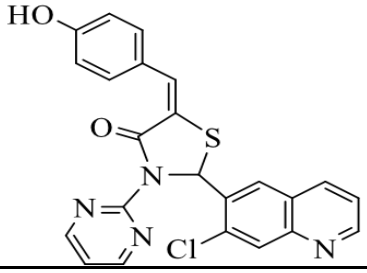
Compound **III** (0.01 mol) was dissolved in ethanol (95%) (20 mL) and benzaldehyde (0.01 mol) was added to it. After the addition of NaOH in catalytic amount, reaction mixture was stirred at 50 °C for 80 min [21–24]. The reaction mixture was then allowed to cool at room temperature. Product was filtered and washed with cold methanol, dried and recrystallized from dimethyl formaldehyde to obtain compound **IV**.

Yield: 62%; m.p.: 217 °C; FTIR (cm^{-1}): 3391 (-CH streching), 1655 (C=O), 1539 (C=N), 851 (=CH), 663 (C-S), 516 (C-Cl); ^{1}H NMR (ppm): 2.4 (s, 1H, -CH), 6.7 (s, 1H, C-H thiazolidinone), 6.9–7.8 (m, 13H, Aromatic); ^{13}C NMR: 37.5 (CH_2), 66.7 (thhiazolidine), 111.8 (p-

benzene), 121.4 (CH=CH), 126.8, 126.9, 127.4, 127.8, 128.2, 128.4, 128.6, 128.8, 128.9, 129.0, 129.1 (CH-Ar), 133.5 (Ar-C-Cl), 135.9 (Ar-CH=C), 139.1 (Ar-C-phenyl), 143.2 (=C-Ar), 151.2 (N=C-Ar), 167.5 (C=O); Anal. Calcd. for $C_{23}H_{15}ClN_4OS$: C-59.36, H-3.03, N-12.04; Found: C-59.45, H-3.12, N-12.13%.

The progress of reaction was monitored by TLC [Aluminium sheet silica gel 60 F254 (E. Merck)] plates using $CHCl_3$:CH_3OH (8.5:1.5) as an irrigator and the plates were visualized with ultraviolet (UV) light, or iodine vapour. All the compounds of series were prepared using the same method.

Table 1. Chemical structures of the newly synthesized compounds.

Sr. No.	R	Chemical Name	Structure
1.	H	5-(benzylidene)-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-one	
2.	4-OCH_3	5-(4-methoxybenzylidene)-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-one	
3.	4-Cl	5-(4-chlorobenzylidene)-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-one	
4.	4-OH	5-(4-hydroxybenzylidene)-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-one	

2.1. Biological Evaluation

2.1.1. Antimicrobial Assay

The synthesized compounds were evaluated against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenes* and strains of fungi *C. albicans*, *A. niger* and *A. clavatus*. The results of antibacterial and antifungal activities for the synthesized compounds are depicted. Minimum inhibition concentration (MIC) values of standard drugs for the comparison of antimicrobial activity of the synthesized compounds are reported.

2.1.2. Antibacterial Assay

Mueller Hinton Broth dilution method (Becton Dickinson, Franklin Lakes, NJ, USA) was used for antibacterial assay of synthesized compounds. The strains obtained from Institute of Microbial Technology, for antibacterial activity. The compounds were tested in triplicate sets for antibacterial activity with different concentration. The drugs which were found to be active in primary analysis were further diluted and evaluated. 10 μg/mL suspensions were further inoculated on appropriate media and the growth was noted after one or two days. Minimum inhibitory concentration is the lowest concentration, which showed no growth of microbes after spot subculture for each drug. The test mixture should contain 108 cells/mL. In this study, Gentamicin, Chloramphenicol, Ciprofloxacin and Norfloxacin were the standard drugs for evaluating the antibacterial activity [21–24].

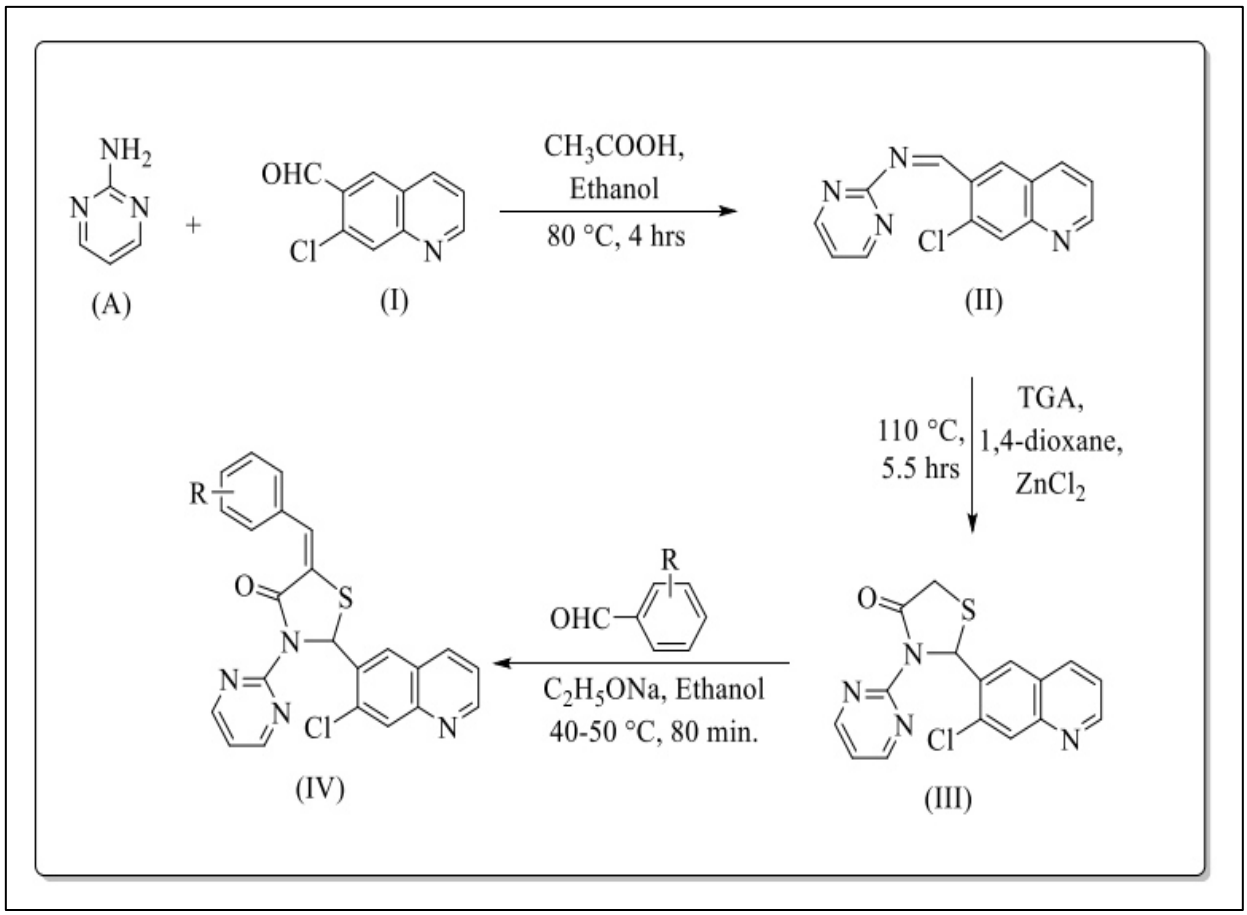
2.1.3. Antifungal Assay

Antifungal activity of the bioactive molecules reported was tested in six sets and the strains reported. The concentrations used for experimentations were 1000, 500 and 250 μg/mL. The compounds which were active in primary screening went for secondary testing, and for secondary testing in a second sets of dilution towards the fungal strains diluted to obtain 200, 125, 62.5, 50, 25, 12.5. The fungal activity of each compound was compared with Nystatin and Griseofulvin as standard drugs. Sabouraud's dextrose broth method was used for the fungal growth at 28 °C in aerobic condition for 48 h. Dimethyl sulphoxide and sterilized distilled water were used as negative control while Nystatin and Griseofulvin (1U strength) were used as a positive control.

3. Result and Discussion

3.1. Chemistry

For the construction of desired 5-arylidene-2-(7-chloroquinolin-6-yl)-3-(pyrimidin-2-yl) thiazolidin-4-ones, the synthetic route of targeted compound is depicted in Scheme 1.



Scheme 1. Synthesis of designed compounds (**IV**).

Biological Evaluation

The synthesized derivatives were screened for their antibacterial and antifungal activity using various strains. The results are depicted in the Table 2.

Table 2. Antimicrobial activity of synthesized compounds.

Sr. No.	R	Minimum Inhibitory Concentration (MIC)						
		Bacteria (μg/mL)				Fungi (μg/mL)		
		E.c.	***P.a.***	***S.a.***	***S.p.***	***C.a.***	***A.n.***	***A.c.***
1.	-H	12.5	62.5	100	200	1000	250	250
2.	4-OCH_3	200	12.5	500	500	>1000	1000	1000
3.	4-Cl	250	200	200	200	100	100	62.5
4.	4-OH	12.5	200	500	500	250	100	100
5.	Gentamicin	0.05	1	0.25	0.5	-	**-**	-
6.	Chloramphenicol	50	50	50	50	-	**-**	-
7.	Ciprofloxacin	25	25	50	50	-	**-**	-
8.	Nystatin	-	-	-	-	100	100	100
9.	Griseofulvin	-	-	-	-	500	100	100

Compound **1** showed prominent activity against *E. coli* and *P. aeruginosa* with MIC value 12.5 and 62.5 μg/mL respectively due to the presence of hydrogen group at 3rd position of benzene ring. It is found to be more active than standard drug. Compound **2** with electron donating group at 3rd position of phenyl ring exhibited potent antibacterial activity with MIC value 12.5 μg/mL.

Electron withdrawing chloro group (-Cl) at 4th position of phenyl ring in compound exhibited potent antifungal activity with MIC value 100 μg/mL for *C. albican* and *A. niger* while the value 62.5 μg/mL was shown for *A. clavatus* compared to standard drug Griseofulvin and Nystatin. The present compound showed potent antibacterial activity due to the presence of electron withdrawing group –OH at 4th position of phenyl ring with MIC value 12.5 μg/mL compared to standard drug against *E. coli*. It also showed potent antifungal activity with MIC value 100 μg/mL for *C. albican* compared to standard drug Griseofulvin.

4. Conclusions

All the synthesized derivatives were meticulously characterized and their structures confirmed through spectroscopic analysis. These compounds exhibited significant activity against both bacterial and fungal agents, highlighting their potential as effective antimicrobial agents. As we continue to face evolving challenges in microbial resistance, these findings underscore the importance of exploring novel therapeutic strategies to safeguard public health.

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Conflicts of Interest:

References

1. Zaffiri, L.; Gardner, J.; Toledo-Pereyra, L.H. History of Antibiotics. From Salvarsan to Cephalosporins. *J. Investig. Surg.* **2012**, *25*, 67–77.
2. Spellberg, B.; Bartlett, J.G.; Gilbert, D.N. The Future of Antibiotics and Resistance. *N. Engl. J. Med.* **2013**, *368*, 299–302.
3. Alanis, A.J. Resistance to Antibiotics: Are We in the Post-Antibiotic Era? *Arch. Med. Res.* **2005**, *36*, 697–705.
4. McGowan, J.E., Jr. Economic Impact of Antimicrobial Resistance. *Emerg. Infect. Dis.* **2001**, *7*, 286–292.
5. Belen'kii, L.I.; Evdokimenkova, Y.B. The Literature of Heterocyclic Chemistry, Part XVII, 2017. *Adv. Heterocycl. Chem.* **2019**, *129*, 337–418.
6. Marson, C.M. Saturated Heterocycles with Applications in Medicinal Chemistry. *Adv. Heterocycl. Chem.* **2017**, *121*, 13–33.
7. Debbabi, M.; Nimbarte, V.D.; Chekir, S.; Chortani, S.; Romdhane, A.; Ben jannet, H. Design and Synthesis of Novel Potent Anticoagulant and Anti-TyrosinasePyranopyrimidines and Pyranotriazolopyrimidines: Insights from Molecular Docking and SAR Analysis. *Bioorg. Chem.* **2019**, *82*, 129–138.
8. Alam, O.; Khan, S.A.; Siddiqui, N.; Ahsan, W.; Verma, S.P.; Gilani, S.J. Antihypertensive Activity of Newer 1,4-Dihydro-5-Pyrimidine Carboxamides: Synthesis and Pharmacological Evaluation. *Eur. J. Med. Chem.* **2010**, *45*, 5113–5119.
9. He, H.; Wang, W.; Zhou, Y.; Xia, Q.; Ren, Y.; Feng, J.; Peng, H.; He, H.; Feng, L. Rational Design, Synthesis and Biological Evaluation of 1,3,4-Oxadiazole Pyrimidine Derivatives as Novel Pyruvate Dehydrogenase Complex E1 Inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 1879–1888.
10. Dube, P.N.; Bule, S.S.; Ushir, Y.V.; Kumbhare, M.R.; Dighe, P.R.; Synthesis of novel 5-methyl pyrazol-3-one derivatives and their in vitro cytotoxic evaluation. *Med. Chem. Res.* **2015**, *24*, 1070–1076.
11. Elsayed, N.M.Y.; Abou El Ella, D.A.; Serya, R.A.T.; Tolba, M.F.; Shalaby, R.; Abouzid, K.A.M. Design, Synthesis and Biological Evaluation of Indazole–Pyrimidine Based Derivatives as Anticancer Agents with Anti-Angiogenic and Antiproliferative Activities. *Medchemcomm* **2016**, *7*, 881–899.
12. Dongre, R.S.; Meshram, J.S.; Selokar, R.S.; Almalki, F.A.; Hadda, T. Ben. Antibacterial Activity of Synthetic Pyrido[2,3-d]Pyrimidines Armed with Nitrile Groups: POM Analysis and Identification of Pharmacophore Sites of Nitriles as Important pro-Drugs. *New J. Chem.* **2018**, *42*, 15610–15617.
13. Dube, P.N.; Mokale, S.N.; Shaikh, S.I.; Patil, Y.; Yadav, B.; Deshmukh, P.; Sabde, S. Synthesis and molecular docking analysis of imidazol-5-one derivatives as anti-HIV NNRTIs. *Pharm. Chem. J.* **2015**, *49*, 125–131.
14. Gaonkar, S.; Savanur, M.A.; Sunagar, M.G.; Puthusseri, B.; Deshapande, N.; Nadaf, A.A.; Khazi, I.A.M. Exploring the Potential of Newly Synthesized 4-Methyl-6-Morpholino-Pyrimidine Derivatives as Antiproliferative Agents. *New J. Chem.* **2018**, *42*, 2790–2803.
15. Banothu, J.; Khanapur, M.; Basavoju, S.; Bavantula, R.; Narra, M.; Abbagani, S. Synthesis, Characterization and Biological Evaluation of Fused Thiazolo[3,2-a]Pyrimidine Derivatives. *RSC Adv.* **2014**, *4*, 22866–22874.
16. Grundon, M.F. Quinoline, Quinazoline, and Acridone Alkaloids. *Nat. Prod. Rep.* **1990**, *7*, 131–138.
17. Dube, P.N.; Bule, S.S.; Mokale, S.N.; Kumbhare, M.R.; Dighe, P.R.; Ushir, Y.V. Synthesis and biological evaluation of substituted 5-methyl-2-phenyl-1*H*-pyrazol-3(2H)-one derivatives as selective COX-2 inhibitors: Molecular docking study. *Chem. Boil. Drug Design* **2014**, *84*, 409–419.
18. Dube, P.N.; Waghmare, M.N.; Mokale, S.N. Synthesis, In Vitro, and In Vivo Biological Evaluation and Molecular Docking Analysis of Novel 3-(3-oxo-substitutedphenyl-3-)4-(2-(piperidinyl)ethoxy)phenyl) propyl)-2H-chromen-2-one Derivatives as Anti-breast Cancer Agents. *Chem. Boil. Drug Design* **2016**, *87*, 608–617.
19. Kamal, A.; Rahim, A.; Riyaz, S.; Poornachandra, Y.; Balakrishna, M.; Kumar, C.G.; Hussaini, S.M.A.; Sridhar, B.; Machiraju, P.K. Regioselective Synthesis, Antimicrobial Evaluation and Theoretical Studies of 2-Styryl Quinolines. *Org. Biomol. Chem.* **2015**, *13*, 1347–1357.
20. Desai, N.C.; Patel, B.Y.; Dave, B.P. Synthesis and Antimicrobial Activity of Novel Quinoline Derivatives Bearing Pyrazoline and Pyridine Analogues. *Med. Chem. Res.* **2017**, *26*, 109–119.
21. Sridhar, P.; Alagumuthu, M.; Arumugam, S.; Reddy, S.R. Synthesis of QuinolineAcetohydrazide-Hydrazone Derivatives Evaluated as DNA Gyrase Inhibitors and Potent Antimicrobial Agents. *RSC Adv.* **2016**, *6*, 64460–64468.
22. Nayak, N.; Ramprasad, J.; Dalimba, U. Synthesis and Antitubercular and Antibacterial Activity of Some Active Fluorine Containing Quinoline–Pyrazole Hybrid Derivatives. *J. Fluor. Chem.* **2016**, *183*, 59–68.
23. Zhao, M.; Kamada, T.; Takeuchi, A.; Nishioka, H.; Kuroda, T.; Takeuchi, Y. Structure–Activity Relationship of IndoloquinolineAnalogs Anti-MRSA. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5551–5554.
24. Dolan, N.; Gavin, D.P.; Eshwika, A.; Kavanagh, K.; McGinley, J.; Stephens, J.C. Synthesis, Antibacterial and Anti-MRSA Activity, in Vivo Toxicity and a Structure–Activity Relationship Study of a Quinoline Thiourea. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 630–635.
25. Musiol, R. An Overview of Quinoline as a Privileged Scaffold in Cancer Drug Discovery. *Expert Opin. Drug Discov.* **2017**, *12*, 583–597.
26. Carmo, A.M.L.; Silva, F.M.C.; Machado, P.A.; Fontes, A.P.S.; Pavan, F.R.; Leite, C.Q.F.; Leite, S.R.d.A.; Coimbra, E.S.; Da Silva, A.D. Synthesis of 4-Aminoquinoline Analogues and Their Platinum(II) Complexes as New Antileishmanial and Antitubercular Agents. *Biomed. Pharmacother.* **2011**, *65*, 204–209.

27. Eswaran, S.; Adhikari, A.V.; Chowdhury, I.H.; Pal, N.K.; Thomas, K.D. New Quinoline Derivatives: Synthesis and Investigation of Antibacterial and Antituberculosis Properties. *Eur. J. Med. Chem.* **2010**, *45*, 3374–3383.
28. Mokale, S.N.; Palkar, A.D.; Dube, P.N.; Sakle, N.S.; Miniyar, P.B. Design, synthesis and in vivo screening of some novel quinazoline analogs as anti-hyperlipidemic and hypoglycemic agents. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 272–276.