Synthesis of N'-(7-Chloroquinolin-4-yl)-6-Methyl-2-Oxo-4-Phenyl-1,2,3,4-Tetrahydropyrimidine-5-Carbohydrazide Derivatives As Potent Antibacterial Agents

Manoj N. Bhoi^a, Mayuri A. Borad^a, Edwin. A. Pithawala^b,
Shweta Modi^a, and Hitesh D. Patel^{a*}

^aDepartment of Chemistry, School of Sciences, Gujarat University, Ahmedabad, India.

^bDepartment of Life Sciences, School of Sciences, Gujarat University, Ahmedabad, India.

E-mail address: hitesh13chem@rediffmail.com Tel.: +91-079-26300969; fax: +91-079-26308545

Keywords: Antibacterial activity, biginelli reaction, Dihydropyrimidines, Quinolines, bacterial strain.

ABSTRACT. Some novel N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide derivatives were synthesized via three step reactions by convectional method. The structures of all the compounds have been confirmed by FT-IR, NMR, and MASS and by elemental analysis. We have been evaluated it inhibition capacity for various gram positive and gram negative bacterial strain. All compounds were found to be good to excellent active against all four bacterial strains.

1. INTRODUCTION

The synthesis of heterocyclic compounds has become one of the key areas of research in the field, both synthetic as well as medicinal chemistry. The most of the compounds with biological activity are derived from heterocyclic structures. Dihydropyrimidines derivative have a diverse and unique place in the medicinal chemistry owing to their wide therapeutic application scenario containing anti-inflammatory agents,[1] anti-bacterial agents,[2] calcium-channel antagonists,[3] antimalarial agents,[4] anti-hypertensive agents,[5] cytotoxic activity,[6] and anti-tubercular agents,[7] etc..

Quinolines is a more important heterocyclic scaffold of paramount importance to the human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Certainly quinolines derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases. Quinolines have caught the attention of researchers owing to their broad range of activities and of course for their wide applications such as antimalarial,[8] Antibacterial,[9] antifungals,[10] anticancer agents,[11] Anti-inflammatory activity, Antiviral, Anti-protozoal, CNS effects, Cardiovascular activity, Analgesic activity, Antineoplastic, Anthelmintic, Hypoglycaemic activity, Reproductive System etc.[12]

Encouraged by their promising medicinal properties of Dihydropyrimidines and Quinoline derivative, we design new compound which contains dihydropyrimidines derivative which linkage with quinolines. So we have synthesised new N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide derivative. Biological activities of newly synthesised dihydropyrimidine derivatives were evaluated under in vitro Antibacterial activity against gram positive and gram negative bacterial strain.

2. MATERIALS AND METHODS

All Starting materials and other reagents were purchased from commercial suppliers and were used without any further purification unless otherwise indicated. The reactions were assayed by thin layer chromatography (TLC) and terminated as judged by the consumption of starting material. Analytical thin-layer chromatography (TLC) was performed on silica gel G 60 F₂₅₄ (Merck) plates.

The melting points were recorded on optimelt automated melting point system and were uncorrected. IR spectra was recorded on a Perkin–Elmer 377 spectrophotometer, ^1H NMR spectra was measured on Bruker AV 400 MHz using DMSO as a solvent and TMS as an internal standard. Mass spectra was recorded on Advion Expression CMS, USA, using Methanol: Water: Formic acid (80: 20: 0.1) as mobile phase. Elemental analysis were performed on the vario MICRO cube, elemental CHN analyser serial no.: 15084053.

General Procedure for the synthesis of compound (4a-4g):

To a stirred mixture of aldehydes derivative (**1a-1g**) (2.0 mmol), ethyl acetoacetate **2** and urea **3** (1.5 mmol) in ethanol solvent in the presence of Alumino silica (10 mol %). The solvent was gradually evaporated by a heating reaction mixture was heated with stirring for 40-55 min. at reflux temperature. Progress of reaction monitored by TLC. After completion of the reaction, cooling the solid precipitate was filtered and washed with cold water and ethanol under reduced pressure and the residue was crystallized from ethanol or ethyl acetate-hexane (1:3) to afford the pure product (**1a-1g**) with very good yields.

General Procedure for the synthesis of compound (5a-5g):

Derivative of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**5a-5g**) was prepared by refluxing a mixture of compound **4a-4g** (0.01 mmol) and hydrazine hydrate 99 % (0.01 mmol) in ethanol for 14 h. The reaction mixture was cooled, dump in cold water and the precipitated solid was collected by filtration, washed with water, dried, and crystallized it.

General Procedure for the synthesis of compound (6a-6g):

6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide derivative (**5a-5g**) (0.01 mmol) and 4,7-dichloroquinoline **6** (0.01 mmol) dissolved in 5 ml CHCl_3 in 25 ml flat bottom flask by using Triethyl amine as a base. The resulting mixture was put in the heated oil bath for 6-8 hrs at reflux temperature. After confirmation of each reaction using TLC analysis (30 % Ethyl acetate: hexane), the reaction mixture was allowed to cool at room temperature and poured into cold water. The mixture was filtered continuously along with a wash of water. The solid crude product was simply purified by column chromatography over silica gel using a solvent system (20 % ethyl acetate: hexane) to obtain subsequent pure product (**7a-7g**) with 70-80 % yield.

N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-

carbohydrazide (7a): IR (KBr) ν_{max} (cm^{-1}): 3056 (C-H Aromatic), 3034 (C-H alkene), 1675 (C=C alkene), 1545 (C=C aromatic), 1659 (C=O amide), 1345 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 8.86 – 8.76 (m, 2H), 8.15 (s, 1H), 8.03 (d, 1H), 7.79 (s, 1H), 7.58 (d, 1H), 7.43 (dd, 1H), 7.29 – 6.75 (m, 5H), 6.72 (d, 1H), 5.56 (s, 1H), 2.42 (s, 1H), 2.32 (s, 3H); ESI-MS: m/z Calculated 407.8, found $[\text{M}+\text{H}]^+$ 408.8; Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{ClN}_5\text{O}_2$: C, 61.84; H, 4.45; Cl, 8.69; N, 17.17; O, 7.85 %; found C, 61.79; H, 4.65; N, 17.34 %.

4-(4-chlorophenyl)-N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-

carbohydrazide (7b): IR (KBr) ν_{max} (cm^{-1}): 3065 (C-H Aromatic), 3075 (C-H alkene), 1634 (C=C alkene), 1509 (C=C aromatic), 1656 (C=O amide), 1350 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.51 – 8.43 (m, 2H), 7.98 (d, 1H), 7.86 (s, 1H), 7.51 (d, 1H), 7.42 (dd, 1H), 7.27 (d, 2H), 7.19 (d, 2H), 6.17 (d, 1H), 5.56 (s, 1H), 4.02 (s, 1H), 2.37 (s, 3H); ESI-MS: m/z Calculated 441.08, found $[\text{M}+\text{H}]^+$ 442.0; Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{N}_5\text{O}_2$: C, 57.03; H, 3.87; Cl, 16.03; N, 15.83; O, 7.23 %; found C, 57.23; H, 3.74; N, 15.65 %.

N'-(7-chloroquinolin-4-yl)-4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro

pyrimidine-5-carbohydrazide (7c): IR (KBr) ν_{max} (cm^{-1}): 3025 (C-H Aromatic), 3046 (C-H alkene), 1656 (C=C alkene), 1486 (C=C aromatic), 1665 (C=O amide), 1354 (C-N Aromatic); ^1H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 8.66 (s, 1H), 8.48 (d, 1H), 7.97 (d, 1H), 7.90 (s, 1H), 7.52 (d, 1H), 7.41 (dd, 1H), 7.06 (d, 2H), 6.59 (d, 2H), 6.21 (d, 1H), 5.56 (s, 1H), 4.03 (s, 1H), 2.88 (s,

6H), 2.35 (s, 3H); ESI-MS: m/z Calculated 450.92, found $[M+H]^+$ 451.9; Anal. Calcd for $C_{23}H_{23}ClN_6O_2$: C, 61.26; H, 5.14; Cl, 7.86; N, 18.64; O, 7.10 %; found C, 61.36; H, 5.26; N, 18.54 %.

N'-(7-chloroquinolin-4-yl)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (7d): IR (KBr) ν_{max} (cm^{-1}): 3077 (C-H Aromatic), 3035 (C-H alkene), 1674 (C=C alkene), 1541 (C=C aromatic), 1671 (C=O amide), 1285 (C-N Aromatic); 1H NMR (400 MHz, DMSO) δ 8.88 (s, 1H), 8.75 (d, 1H), 8.61 (s, 1H), 8.11 (dt, 1H), 8.02 (d, 2H), 7.76 – 7.63 (m, 3H), 7.53 – 7.44 (m, 2H), 6.63 (d, 1H), 5.56 (s, 1H), 2.76 (s, 1H), 2.36 (s, 3H); ESI-MS: m/z Calculated 452.8, found $[M+H]^+$ 453.8; Anal. Calcd for $C_{21}H_{17}ClN_6O_4$: C, 55.70; H, 3.78; Cl, 7.83; N, 18.56; O, 14.13 %; found C, 55.55; H, 3.69; N, 18.45 %.

N'-(7-chloroquinolin-4-yl)-4-(3,4-dihydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (7e): IR (KBr) ν_{max} (cm^{-1}): 3063 (C-H Aromatic), 3065 (C-H alkene), 1652 (C=C alkene), 1590 (C=C aromatic), 1681 (C=O amide), 1279 (C-N Aromatic); 1H NMR (400 MHz, DMSO) δ 8.85 (s, 1H), 8.76 (d, 1H), 8.31 (s, 1H), 8.10 (s, 1H), 8.02 (d, 1H), 7.82 (s, 1H), 7.61 (d, 1H), 7.48 – 7.41 (m, 2H), 6.73 (dd, 1H), 6.64 (dd, 2H), 6.47 (d, 1H), 5.56 (s, 1H), 2.43 (s, 1H), 2.34 (s, 3H); ESI-MS: m/z Calculated 439.85, found $[M+H]^+$ 440.8; Anal. Calcd for $C_{21}H_{18}ClN_5O_4$: C, 57.34; H, 4.12; Cl, 8.06; N, 15.92; O, 14.55 %; found C, 57.46; H, 4.32; N, 15.85 %.

4-(3-chlorophenyl)-N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (7f): IR (KBr) ν_{max} (cm^{-1}): 3037 (C-H Aromatic), 3025 (C-H alkene), 1651 (C=C alkene), 1489 (C=C aromatic), 1674 (C=O amide), 1365 (C-N Aromatic); 1H NMR (400 MHz, DMSO) δ 8.69 (d, 2H), 8.06 – 7.95 (m, 2H), 7.87 (s, 1H), 7.69 (d, 1H), 7.46 (dd, 1H), 7.41 – 7.24 (m, 4H), 6.43 (d, 1H), 5.27 (s, 1H), 2.13 (s, 3H), 1.38 (s, 1H); ESI-MS: m/z Calculated 442.3, found $[M+H]^+$ 443.3; Anal. Calcd for $C_{21}H_{17}Cl_2N_5O_2$: C, 57.03; H, 3.87; Cl, 16.03; N, 15.83; O, 7.23 %; found C, 57.19; H, 3.78; N, 15.86 %.

N'-(7-chloroquinolin-4-yl)-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (7g): IR (KBr) ν_{max} (cm^{-1}): 3089 (C-H Aromatic), 3060 (C-H alkene), 1629 (C=C alkene), 1587 (C=C aromatic), 1675 (C=O amide), 1387 (C-N Aromatic); 1H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 8.69 (d, 1H), 8.37 (s, 1H), 8.11 (dd, 4.4 Hz, 3H), 7.79 – 7.70 (m, 2H), 7.53 – 7.39 (m, 3H), 6.55 (d, 1H), 5.56 (s, 1H), 2.84 (s, 1H), 2.35 (s, 3H); ESI-MS: m/z Calculated 452.85, found $[M+H]^+$ 453.8; Anal. Calcd for $C_{21}H_{17}ClN_6O_4$: C, 55.70; H, 3.78; Cl, 7.83; N, 18.56; O, 14.13 %; found C, 55.86; H, 3.72; N, 18.78 %.

Antibacterial Activity

Antibacterial activities of **7a-7g** were carried out in Nutrient-agar plates by well diffusion assay. Cultures were activated in Nutrient broth. Isolates were inoculated in Nutrient broth and incubated at 37 °C for 24 hours for activation of cultures and then centrifuged at 3000 rpm for 15 min and the supernatant was collected to study antibacterial activity.

Using *in-vitro* agar well diffusion method, antimicrobial activity experiments were carried out. The activity of **7a-7g** against test microorganisms (1000 μ l volume with 1000 μ g/ml concentration) of activated test cultures 2 Gram negative and 2 Gram positive; viz. *Enterobacter aerogens* MTCC No. 8558, *Escherichia coli* MTCC No. 1610, *Micrococcus luteus* MTCC No. 11948 and *Bacillus cereus* MTCC No. 8557) was inoculated in molten agar and poured into sterile plates than allowed to solidify. Wells with 5mm diameter were prepared at equal distance in solidified agar plates using cup-borer. Various derivatives **7a-7g** with 1000 μ g/ml concentration were inoculated in the wells of nutrient agar whereas test microorganisms were inoculated by pour plate technique. The plates were incubated at 37 °C for 24 hours. The inhibition zones were measured at the end of the incubation period.

3. RESULT AND DISCUSSION

3.1. Chemistry

The title compounds, *N'*-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide derivative (**7a-7g**) were synthesized via three step reactions from biginelli reaction reaction, hydrazine hydrate and 4,7-dichloro Quinoline as outlined in scheme 1.

Biginelli reaction is a versatile method for the preparation of Dihydropyrimidines derivative by reaction between aldehydes derivative (**1a-1g**), ethyl acetoacetate **2** and urea **3** in ethanol solvent in the presence of Alumino silica (10 mol %) as prompt catalyst. As per literature survive, here we first time reported Alumino silica catalysed synthesis of Dihydropyrimidines derivative.

Scheme 1 synthesis of targeted compound **7a-7g**

As shown in Table 1, it was found that this method works with a wide variety of substrates. A series of different position substituted benzaldehyde including either electron-withdrawing or electron-donating groups were used in this reaction, in good yields (70-80%).

Table 1 Synthesis of *N'*-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carbohydrazide derivative **7a-7g**

Entry	2-amino benzothiazole derivative	Product	yield %	mp °C
1	 1a	 7a	75.8	177-178

2	<p>1b</p>	<p>7b</p>	73.6	174-177
3	<p>1c</p>	<p>7c</p>	76.4	173-175
4	<p>1d</p>	<p>7d</p>	80.1	175-176
5	<p>1e</p>	<p>7e</p>	73.4	172-175
6	<p>1f</p>	<p>7f</p>	74.8	175-179
7	<p>1g</p>	<p>7g</p>	70.5	172-176

The structure of the compound **7a** was explained with the help of IR, ^1H NMR, mass spectral data, and elemental analysis. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values at 408.8 mass unit. The IR spectra of compounds **7a** exhibited peaks at strong amide ($\text{C}=\text{O}$) stretching band at 1659 cm^{-1} . $\text{C}=\text{C}$ and $\text{C}-\text{H}$ aromatic stretching band was observed at 1675 and 3056 cm^{-1} respectively. ^1H NMR spectrum of **7a** shows peaks at 8.86, δ value resulting from $-\text{NH}$ of dihydropyrimidine ring. Amide type proton resonate in ^1H NMR at

8.15 δ ppm. Aromatic proton of targeted compound resonates at 7.5– 6.72 δ ppm. Rest of all proton resonated at 5.56, 2.42, 2.32 δ ppm.

3.2. Biology

Antibacterial Activity

All the compounds (**7a–7g**) were screened for their antibacterial activity out on Nutrient-agar plates by well–diffusion assay against test culture. Cultures were stimulated in Nutrient broth. Isolates inhibits the above mentioned organisms or not were studied. A zone of inhibition was measured in terms of zone diameter and with the help of that zone index was calculated by using streptomycin as a standard drug. Compounds **7a–7g** were screened against *Enterobacter aerogens* (MTCC 8558), *Escherichia coli* (MTCC 1610), *Micrococcus luteus* (MTCC 11948), and *Bacillus cereus* (MTCC 8558). The results are illustrated in Table 3.

Table 2 Antibacterial Activity of synthesized compounds **7a–7g**

Derivatives	<i>Enterobacter aerogens</i> MTCC No. 8558		<i>Escherichia coli</i> MTCC No. 1610		<i>Micrococcus luteus</i> MTCC No. 11948		<i>Bacillus cereus</i> MTCC No. 8558	
	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)	Mean value for Zone of Inhibition (mm)	Activity Index (A.I.)
7a	21	0.875	22	0.916	23	0.958	23	0.958
7b	19	0.791	24	1.000	21	0.875	21	0.875
7c	20	0.833	23	0.958	22	0.916	24	1.000
7d	24	1.000	24	1.000	24	1.000	25	1.041
7e	25	1.041	20	0.833	25	1.041	22	0.916
7f	21	0.875	21	0.875	24	1.000	24	1.000
7g	18	0.750	22	0.916	22	0.916	23	0.958
Std drug	24	---	24	---	24	---	24	---

Determination of activity index

The activity index of the probiotic culture was calculated as:

$$\text{Activity index (A.I.)} = \frac{\text{Mean of zone of inhibition of derivative}}{\text{Zone of inhibition obtained for standard antibiotic drug}}$$

Note: Standard drug used was Streptomycin with 1000 $\mu\text{g/ml}$ concentration

The antibacterial activity data revealed that almost all the compounds **7a–7g** exhibited promising antibacterial activity against gram negative and gram positive bacteria compared to streptomycin standard drug. Compounds **7d–7f** exhibited better zone of inhibition against *Enterobacter aerogens* gram negative bacteria. When compound **7a–7g** shows 87.5 % zone of inhibition to standard drug

against *Escherichia coli*. For *Micrococcus luteus*, compounds **7d-7f** found to be very active than all other compounds in the series. Moreover, the compounds **7c**, **7d**, and **7f** displayed good activity against *Bacillus cereus* gram positive bacteria.

4. CONCLUSION

In this article, we have presented the initial efforts made toward the synthesis of novel, potentially active N'-(7-chloroquinolin-4-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide derivatives. These derivatives were prepared through three step reaction of biginelli reaction, hydrazine hydrate and 4,7-dichloro Quinoline. When compound **7a-7g** shows 87.5 % zone of inhibition to standard drug against *Escherichia coli*. Compounds **7d-7f** exhibited better zone of inhibition against *Enterobacter aerogens* gram negative bacteria. For *Micrococcus luteus*, compounds **7d-7f** found to be very active than all other compounds in the series. Moreover, the compounds **7c**, **7d**, and **7f** displayed good activity against *Bacillus cereus* gram positive bacteria. Finally, it is conceivable that further derivatization of such compounds will be of interest with good hope to get more selective antibacterial agents.

Acknowledgement

The authors are thankful to UGC-Info net and INFLIBNET Gujarat University for providing e-source facilities. Both Mayuri A. Borad and Manoj N. Bhoi is thankful to *UGC-BSR* fellowship for financial assistance.

References

- [1] (a) SS. Bahekar, DB. Shinde, Synthesis and anti-inflammatory activity of some [4, 6-(4-substituted aryl)-2-thioxo-1, 2, 3, 4-tetrahydro-pyrimidin-5-yl]-acetic acid derivatives. *Bioorg. Med. Chem. Lett.*, 14 (2004), 1733-1736; (b) SN. Mokale, SS. Shinde, RD. Elgire, JN. Sangshetti, DB. Shinde, Synthesis and anti-inflammatory activity of some 3-(4, 6-disubstituted-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl) propanoic acid derivatives. *Bioorg. Med. Chem. Lett.*, 20 (2010), 4424-4426.
- [2] (a) M. Kidwai, S. Saxena, MKR. Khan, S. Thukral, Synthesis of 4-aryl-7, 7-dimethyl-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline-2-one/thione-5-one derivatives and evaluation as antibacterials. *Eur. J. Med. Chem.*, 40 (2005), 816-819; (b) M. Ashok, BS. Holla, NS. Kumari, Convenient one pot synthesis of some novel derivatives of thiazolo [2, 3-b] dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluation of their antibacterial and antifungal activities. *Eur. J. Med. Chem.*, 42 (2007), 380-385; (c) M. Deshmukh, S. Salunkhe, D. Patil, P. Anbhule, A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines and their anti-bacterial activity. *Eur. J. Med. Chem.*, 44 (2009), 2651-2654; (d) S. Chitra, D. Devanathan, K. Pandiarajan, Synthesis and in vitro microbiological evaluation of novel 4-aryl-5-isopropoxycarbonyl-6-methyl-3, 4-dihydropyrimidinones. *Eur. J. Med. Chem.*, 45 (2010), 367-371.
- [3] (a) H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, Dihydropyrimidines: novel calcium antagonists with potent and long-lasting vasodilative and anti-hypertensive activity. *J. Med. Chem.*, 32 (1989), 2399-2406; (b) KS. Atwal, GC. Rovnyak, SD. Kimball, DM. Floyd, S. Moreland, BN. Swanson, JZ. Gougoutas, J. Schwartz, KM. Smillie, MF. Malley, Dihydropyrimidine calcium channel blockers. II. 3-Substituted-4-aryl-1, 4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. *J. Med. Chem.*, 33 (1990), 2629-2635.

- [4] AN. Chiang, JC. Valderramos, R. Balachandran, RJ. Chovatiya, BP. Mead, C. Schneider, SL. Bell, MG. Klein, DM. Huryn, XS. Chen, Select pyrimidinones inhibit the propagation of the malarial parasite, *Plasmodium falciparum*. *Bioorg. Med. Chem.*, 17 (2009), 1527-1533.
- [5] (a) IS. Zorkun, S. Saraç, S. Çelebi, K. Erol, Synthesis of 4-aryl-3, 4-dihydropyrimidin-2 (1H)-thione derivatives as potential calcium channel blockers. *Bioorg. Med. Chem.*, 14 (2006), 8582-8589; (b) CA. Sehon, GZ. Wang, AQ. Viet, KB. Goodman, SE. Dowdell, PA. Elkins, SF. Semus, C. Evans, LJ. Jolivet, RB. Kirkpatrick, Potent, selective and orally bioavailable dihydropyrimidine inhibitors of Rho kinase (ROCK1) as potential therapeutic agents for cardiovascular diseases. *J. Med. Chem.*, 51 (2008), 6631-6634; (c) R. Chikhale, R. Bhole, P. Khedekar, K. Bhusari, Synthesis and pharmacological investigation of 3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates. *Eur. J. Med. Chem.*, 44 (2009), 3645-3653; (d) O. Alam, SA. Khan, N. Siddiqui, W. Ahsan, SP. Verma, SJ. Gilani, Antihypertensive activity of newer 1, 4-dihydro-5-pyrimidine carboxamides: Synthesis and pharmacological evaluation. *Eur. J. Med. Chem.*, 45 (2010), 5113-5119.
- [6] BP. Kumar, G. Sankar, RN. Baig, S. Chandrashekar, Novel Biginelli dihydropyrimidines with potential anticancer activity: a parallel synthesis and CoMSIA study. *Eur. J. Med. Chem.*, 44 (2009), 4192-4198.
- [7] (a) V. Virsodia, RR. Pissurlenkar, D. Manvar, C. Dholakia, P. Adlakha, A. Shah, EC. Coutinho, Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxamides. *Eur. J. Med. Chem.*, 43 (2008), 2103-2115; (b) AR. Trivedi, VR. Bhuva, BH. Dholariya, DK. Dodiya, VB. Kataria, VH. Shah, Novel dihydropyrimidines as a potential new class of antitubercular agents. *Bioorg. Med. Chem. Lett.*, 20 (2010), 6100-6102.
- [8] (a) O. Billker, V. Lindo, M. Panico, A. Etienne, T. Paxton, A. Dell, M. Rogers, R. Sinden, H. Morris, Identification of xanthurenic acid as the putative inducer of malaria development in the mosquito. *Nature*, 392 (1998), 289-292; (b) G. Roma, M. Di Braccio, G. Grossi, F. Mattioli, M. Ghia, 1, 8-Naphthyridines IV. 9-Substituted N, N-dialkyl-5-(alkylamino or cycloalkylamino)[1, 2, 4] triazolo [4, 3-a][1, 8] naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. *Eur. J. Med. Chem.*, 35 (2000), 1021-1035; (c) P. Winstanley, Chemotherapy for falciparum malaria: the armoury, the problems and the prospects. *Parasitology Today*, 16 (2000), 146-153; (d) YL. Chen, KC. Fang, JY. Sheu, SL. Hsu, CC. Tzeng, Synthesis and antibacterial evaluation of certain quinolone derivatives. *J. Med. Chem.*, 44 (2001), 2374-2377.
- [9] (a) KC. Fang, YL. Chen, JY. Sheu, TC. Wang, CC. Tzeng, Synthesis, antibacterial, and cytotoxic evaluation of certain 7-substituted norfloxacin derivatives. *J. Med. Chem.*, 43 (2003), 3809-3812; (b) J. Chevalier, S. Atifi, A. Eyraud, A. Mahamoud, A. Barbe, JM. Pagès, New Pyridoquinoline Derivatives as Potential Inhibitors of the Fluoroquinolone Efflux Pump in Resistant *Enterobacter aerogenes* Strains. *J. Med. Chem.*, 44 (2001), 4023-4026; (c) LT. Phan, T. Jian, Z. Chen, YL. Qiu, Z. Wang, T. Beach, A. Polemeropoulos, YS. Or, Synthesis and antibacterial activity of a novel class of 4'-substituted 16-membered ring macrolides derived from tylosin. *J. Med. Chem.*, 47 (2004), 2965-2968; (d) SJ. Benkovic, SJ. Baker, M. Alley, YH. Woo, YK. Zhang, T. Akama, W. Mao, J. Baboval, PR. Rajagopalan, M. Wall, Identification of borinic esters as inhibitors of bacterial cell growth and bacterial methyltransferases, CcrM and MenH. *J. Med. Chem.*, 48 (2005), 7468-7476.

-
- [10] MAV. Castelli, VV. Kouznetsov, SN. López, M. Sortino, RD. Enriz, JC. Ribas, S. Zacchino, In vitro antifungal activity of new series of homoallylamines and related compounds with inhibitory properties of the synthesis of fungal cell wall polymers. *Bioorg. Med. Chem.*, 11 (2003), 1531-1550.
- [11](a) L. Dassonneville, K. Bonjean, MC. De Pauw-Gillet, P. Colson, C. Houssier, J. Quetin-Leclercq, L. Angenot, C. Bailly, Stimulation of topoisomerase II-mediated DNA cleavage by three DNA-intercalating plant alkaloids: cryptolepine, matadine, and serpentine. *Biochemistry*, 38 (1999), 7719-7726; (b) C. Bailly, W. Laine, B. Baldeyrou, MC. De Pauw-Gillet, P. Colson, C. Houssier, K. Cimanga, S. Van Miert, AJ. Vlietinck, L. Pieters, DNA intercalation, topoisomerase II inhibition and cytotoxic activity of the plant alkaloid neocryptolepine. *Anti-cancer drug design*, 15 (2000), 191-201; (c) L. Dassonneville, A. Lansiaux, A. Wattelet, N. Wattez, C. Mahieu, S. Van Miert, L. Pieters, C. Bailly, Cytotoxicity and cell cycle effects of the plant alkaloids cryptolepine and neocryptolepine: relation to drug-induced apoptosis. *Euro. J. Pharm*, 409 (2000), 9-18; (d) SY. Ablordeppey, P. Fan, S. Li, AM. Clark, CD. Hufford, Substituted indoloquinolines as new antifungal agents. *Bioorg. Med. Chem.*, 10 (2002), 1337-1346.
- [12] A. Marella, OP. Tanwar, R. Saha, MR. Ali, S. Srivastava, M. Akhter, M. Shaquiquzzaman, MM. Alam, Quinoline: A versatile heterocyclic. *Saudi Pharmaceutical Journal*, 21 (2013), 1-12.