ISSN No:-2456-2165

Design, Synthesis and Characterization of Anti-Malarial Agent (Ethyl 6-Methyl-4-(Quinolin-8-Yloxy) Quinoline-3-Carboxylate)

Sheeraz Khan Rasheedy, Azizulhaq Afgar
Department of Chemistry
Sayed Jamaluddin Afghani University
Kunar, Afghanistan

Abstract:- The greater part of the total populace live in regions where they stay in danger of jungle fever disease. During last years, the circumstance has deteriorated in numerous ways, mostly because of malarial parasites turning out to be progressively impervious to a few antimalarial drugs. Jungle fever actually stays one of the most perilous broad parasitic illnesses of the creating scene in spite of the fact that it is known to humanity since old times in various structures, and exists north of 100 nations, including the United States. We plan and incorporate medications atoms with high power than the recently revealed ones. Synthesis of particles with least expense and serious level of efficacy. Synthesis of the medication particles with making least side impacts.

Keywords:- *Docking, ^{1}HNMR. ^{13}CNMR and HRMS.*

I. INTRODUCTION

developed with time separating into four unmistakable species: P. falciparum, P. vivex, P. malarae and P. ovale, intended for people. A few other related animal groups including P. berghii and P. yeolii are intended for different gatherings of the mammalian class [17].

The World Health Organization (WHO) detailed the event of 214 million cases overall in 2015, and the demise of 438,000 individuals, generally youngsters in the African district [19].Among the different types of Plasmodium, P. falciparum is the most deadly one causing the most destructive type of human jungle fever; bringing about 200-300 million diseases and 1-3 million passings, every year [3]. Throughout the course of recent many years, the rapid development of medication safe strains has intensified the all around serious medical issues. Of the four known human jungle fever parasites, Plasmodium falciparum is the transcendent reason for mortality, with 120 million new cases and 1 million passings each year globally[2].

It is this specific species, which has led to considerable medication safe strains, bringing about the pressing requirement for new chemotherapeutic specialists. The quest for new specialists has as of late been supported with the consummation of the P. falciparum genome.3 Detailed studies4 of this genome have recognized new possible medication and antibody targets. One such objective gives off an impression of being unsaturated fat biosynthesis of P. falciparum [17]. It has been accounted for to taint human populaces for north of 50,000 years [5]. The main proof of Plasmodium was accounted for in a fossilized Culex mosquito in a piece of golden, very nearly 30 million years of age [6].

As of now, a few medications like chloroquine (CQ), amodiaquine, pyrimethamine, proguanil, mefloquine, atovaquone, primaquine, and so on. (Fig. 1.1) are accessible in market for the treatment of jungle fever. The primary objective of the greater part of the antimalarial drugs is the erythrocytic phase of malarial disease. From the most recent twenty years, the obstruction of P. falciparum strains to CQ and the antifolate mix of sulfadoxine/pyrimethamine prompted artemisinin mix treatment (ACT), [7] which is presently an overall treatment of simple intestinal sickness [8].

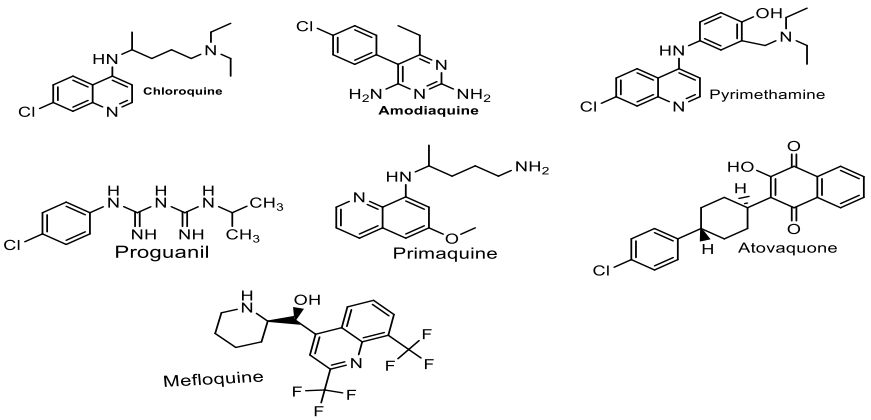


Fig. 1: Some of the market available antimalarial

ISSN No:-2456-2165

Jungle fever has been portrayed as a worldwide scourge sickness that has been known in China, Mesopotamia and Egypt beginning around 2700, 2000 and 1570 BCs, separately [9]. The jungle fever parasite is a Plasmodium protozoan animal categories, which developed with time separating into four unmistakable species: P. falciparum, P. vivex, P. malarae and P. ovale, well defined for people. A few other related animal types including P. berghii and P. yeolii are well defined for different gatherings of the mammalian class[18].

The existence pattern of intestinal sickness parasite P. falciparum is perplexing that consolidates different intra and extra cell conditions. It incorporates three sub-cycles, one happening in the vector called sporogonic cycle and two in the human host called exo-erythrocytic cycle and erythrocytic cycle.Human jungle fever is brought about by four distinct types of Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale and Plasmodium vivax[12]. Different side effects shown by patients impacted by jungle fever are Running nose, hack and different indications of respiratory contamination, Diarrhea/looseness of the bowels, Burning micturition or potentially lower stomach pain,Skin rash/diseases, Abscess, Painful expanding of joint, Ear discharge[14].

II. TREATMENT

Intestinal sickness is treated with antimalarial prescriptions; the ones utilized relies upon the sort and seriousness of the illness. While meds against fever are regularly utilized, their consequences for results are not satisfactory [15].Uncomplicated intestinal sickness might be treated with oral drugs. The best treatment for P. falciparum contamination is the utilization of artemisinins in mix with different antimalarials (known as artemisinin-mix treatment, or ACT), which diminishes protection from any single medication part [12].

To treat jungle fever during pregnancy, the WHO suggests the utilization of quinine in addition to clindamycin right off the bat in the pregnancy (first trimester), and ACT in later stages (second and third trimesters) [7]. Disease with P. vivax, P. ovale or P. malariae is typically treated without the requirement for hospitalization. Treatment of P. vivax requires both treatment of blood stages (with chloroquine or ACT) and leeway of liver structures with primaquine [13].Recommended treatment for extreme intestinal sickness is the intravenous utilization of antimalarial drugs. For extreme jungle fever, artesunate is better than quinine in the two youngsters and grown-ups [11].

III. MEDICINES

Meds to treat jungle fever have been around for millennia. Maybe the most popular of the conventional cures is quinine, which is gotten from the bark of the cinchona tree. Commodity of quinine to Europe, and later the United States, was a rewarding business until World War II slice off admittance to the world stockpile of cinchona bark. During the 1940s, an escalated research program to find options in contrast to quinine brought about the assembling of chloroquine and various other synthetic mixtures that turned into the trailblazers of present day antimalarial drugs. Chloroquine was the third most generally involved drug on the planet until the mid-1990s. It is modest to fabricate, simple to give, and doesn't create issues for the vast majority. Sadly, chloroquine-safe jungle fever parasites have created and have spread to mostareas of the world. From the 1950s to the present, chloroquine opposition step by step spread to essentially all P. falciparum intestinal sickness endemic districts.

During the 1960s, many specialists treating individuals in Asia were utilizing one more new group of medications in view of the parent drug artemisinin, a concentrate of the Chinese natural cure qinghaosu. Tragically, jungle fever parasites in numerous geographic districts have become impervious to elective medications, large numbers of which were found exclusively over the most recent 30 years. Indeed, even quinine, the enduring backbone of jungle fever treatment, is losing its adequacy in specific regions. To resolve the issue of medication safe intestinal sickness [14], researchers are leading examination on the hereditary systems that empower Plasmodium parasites to stay away from the harmful impacts of jungle fever drugs. Understanding how those instruments work ought to empower researchers to foster new medications or modify existing ones to make drug obstruction more troublesome.

Intestinal sickness parasites attack different tissues like skin, blood, liver, stomach, and salivary organs of human and mosquito has, and that implies the parasites should have the option to connect to a different exhibit of particles or receptors outwardly of host cells. By deciding the three-layered designs of these receptors, researchers desire to decide precisely the way that the parasites target specific kinds of cells, which might uncover new focuses for antimalarial drugs.

NIAID researchers are likewise attempting to figure out how P. falciparum has adjusted to make due and develop inside RBCs. They might have the option to configuration channel blockers that obstruct the parasite's capacity to gain required supplements. These blockers might end up being novel and valuable medications for treating jungle fever.

IV. DESIGN OF MOLECULES

A. *What is PfPMT?*

- Plasmodium falciparum Phosphoethanolamine Methyltransferase (*Pf*PMT) is S-adenosyl methamine (SAM) dependent methyl transferase that catalyses phosphoethanolamine (pEa) to phosphocoline.
- *Pf*PMT is essential for the normal growth and survival of the Plasmodium which is not found in humans is a viable target.

ISSN No:-2456-2165

B. PfPMT Inhibitors

- The inhibitor or enzyme inhibitor is a molecule that binds to the active site of an enzyme and decreases its activity. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance. many drugs are enzyme inhibitors.

C. Docking Protocol

The docking and scoring of ligands with PfPMT. Proteins are achieved utilizing pardock module of sanjeevini drug plan suite which depends on physic-compound descriptors. We involved docking module for the planning of reference protein intricate as an info document. Docking of ligand particle at the dynamic site depression of PfPMT was finished by utilizing all molecule energy based Monte Carlo calculation which limits and scores the docked complex. The molecule was designed and docked with freely accessible software called ParDOCK, available at IIT, Delhi. The crystal structure of protein is ***PfPMT*** which is docked with synthesized compound. The PDB ID of ***PfPMT*** is 3UJB.

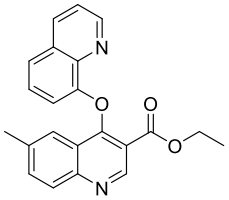
Name of compound	Synthesized Compound	Free energy value (kcal/mol)	logP
ethyl 6-methyl-4-(naphthalen-8-yloxy)quinoline-3-carboxylate		**-7.36**	**4.80**

Table 1: Binding free energy and logP value of the docked compound by Pardock

- **Docked view of ethyl 6-methyl-4-(naphthalen-8-yloxy)quinoline-3-carboxylate with *Pf*PMT.**

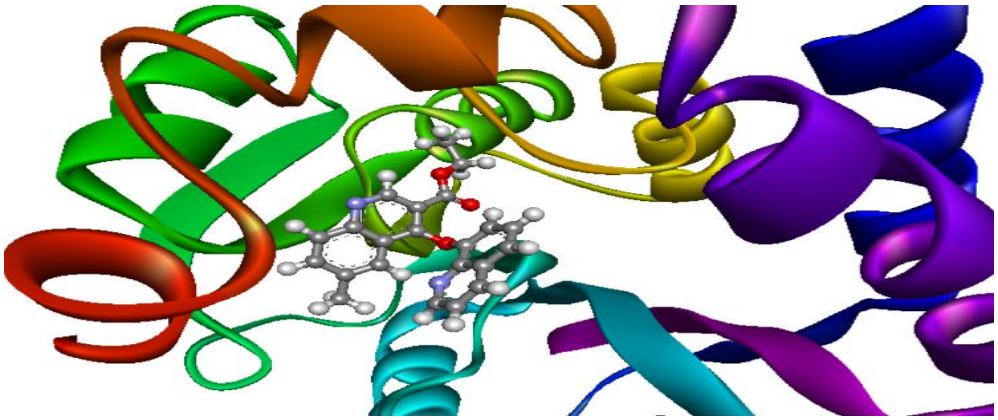


Fig. 2

The free energy value of 5a docked with *Pf*PMT is **-7.36** kcal/mol.

V. RESULT AND DISCUSSION

A. Chemistry

The synthesis of target molecule was achieved by multistep reactions which are outlined in **Scheme1**. First of all, diethyl ethoxymethylenemalonate was treated with different aniline at ambient temperature in presence of benzene to obtain compound 3. Secondly,$POCl_3$ was added to the compound 3 and and refluxed for 18 h for the cyclization of the compound called, Vilsmeier-Haack reaction to get the compound 4. Finally compound 4 undergo nucleophilic aromatic substitution reaction with p-toludine and p-anisidine to give the desired final compound as 5. Finally, all the newly synthesized compound was verified by different spectroscopic techniques I.e. ^{1}H NMR, ^{13}C NMR and HRMS.

B. Objectives Of Work

- To design and synthesize drugs molecules with high potency than the previously reported ones.
- Synthesis of molecules with minimum cost and high degree of efficacy.
- Synthesis of the drug molecules with having least side effects.

VI. METHODOLOGY

- Synthesis of the designed compounds using organic protocol.
- Spectral techniques *viz.* ^{1}HNMR, ^{13}CNMR and HRMS has been used for the characterization of newly synthesized compound.
- **Experimental Section**
- **Experimental Protocol**

ISSN No:-2456-2165

VII. MATERIALS AND METHODS

Melting point of the synthesized compounds were determined in pyrex capillaries using a basic melting apparatus and were uncorrected. All required chemicals were purchased from Spectrochem and Sdfine chemicals Pvt. Ltd. India, and were used as received. Precoated aluminium sheet (silica gel 60 F254, Merck Germany) were used for thin layer chromatography (TLC) and spots were visualized under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrospin DPX 400 MHz using DMSO and $CDCl_3$ as solvent and TMS as an internal standard.

- **Scheme for the synthesis of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate**

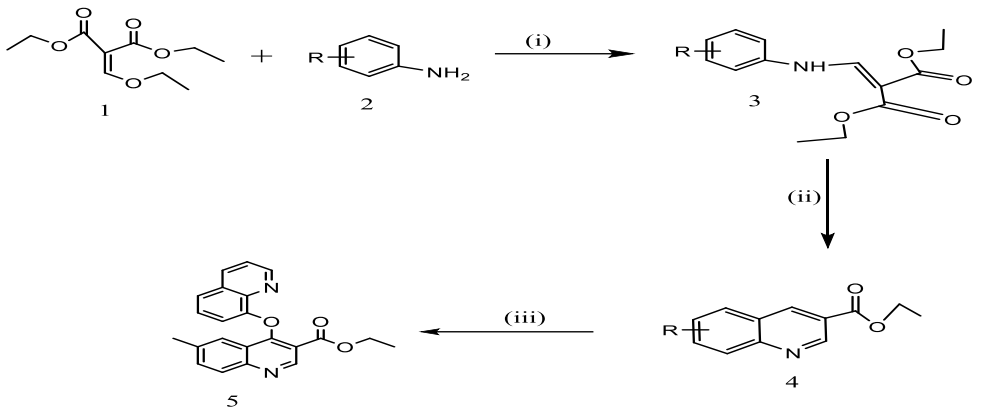


Fig. 3

- **Reagents and conditions:** 1= Diethyl ethoxymethylenemalonate, R= p-anisidine, p-toluidine; (i) Benzene, 83 °C; (ii) $POCl_3$, 110 °C; (iii) 8-OH Quinoline, DMF, t-BuO-K+, 120 °C..

- **Procedure:**
  - **Methods for the preparation of compound 3**
    Diethyl (ethoxymethylene) malonate (25 mmol) and substituted aniline (25 mmol) were mixed in equivalent proportions at ambient temperature, giving rise to an exotherm of 18 °C. Benzene (6.5 ml) was added and the resulting solution heated under reflux (83 °C) for 1.5 h. The solution was concentrated in vacuo to obtain an oil, which was crystallized on standing. The crude product was slurried in hexane, filtered off and air dried to give the compound 3 (m.p. 47-50 °C).

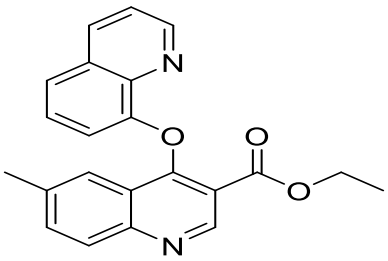
  - **Methods of preparation of compound 4**
    A solution of 3 (85 mmol) in $POCl_3$ (1.34 mol) was heated under reflux for 18 h. The cooled solution was concentrated in vacuo and the resulting brown oil partitioned between dichloromethane (500 ml) and water (250 ml). Organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil, which was purified by column chromatography eluted with 17% EtOAc/Hexane to obtain compound4.

  - **Synthesis of ethyl 6-methyl-4-(quinolin-8-yloxy)quinoline-3-carboxylate (5)**
    A mixture of compound **4** (1.2 equiv.), 8-hydroxyquinoline (1.0 g) and t-BuO-K (1.2 equiv.) in anhydrous DMF was added to the room temperature and was reflux at 120-130 °C for 6-8 hrs. After the completion of reaction monitored by TLC, the reaction mixture was cooled to room temperature. Water was added to the reaction mixture and extracted with ethyl acetate (2’ 75). The combined organic layers were washed with brine, dried over Na2SO4, and evaporated to yield the crude product, which was purified by column chromatography and eluted with EtOAc/hexane to give compound **5 as** off white solid; yield: 68%; mp: 270-280 oC; 1H NMR (400 MHz, CDCl3) δ 9.332 (1H), 9.02 (1H), 8.23 (2H), 7.70 (1H), 7.55 (1H), 7.53 (2H), 7.30 (1H), 6.87 (1H), 3.92 (2H), 2.44 (3H, p-Toluidine), 0.68 (3H, CH3). 13C NMR (100MHz, CDCl3) δ 163.77, 160.53, 154.53, 150.33, 150.15, 148.43, 139.12, 138.59, 136.30, 135.33,129.83, 128.01, 126.55, 123.34, 122.55, 122.42, 122.30, 115.71, 112.39, 61.60, 21.85, 13.40.

    HRMS (TOF) Calcd. for C22H18N2O3Na [M+Na]+, 381.1215; found, 381.1215.

VIII. CHARACTERIZATION

Synthesized compound are characterized by ^{1}H NMR, ^{13}C NMR and HRMS Spectral studies



ethyl 6-methyl-4-(quinolin-8-yloxy)quinoline-3-carboxylate

Fig. 4

^{1}H NMR of ethyl 6-methyl-4-(naphthalen-8-yloxy)quinoline-3-carboxylate.

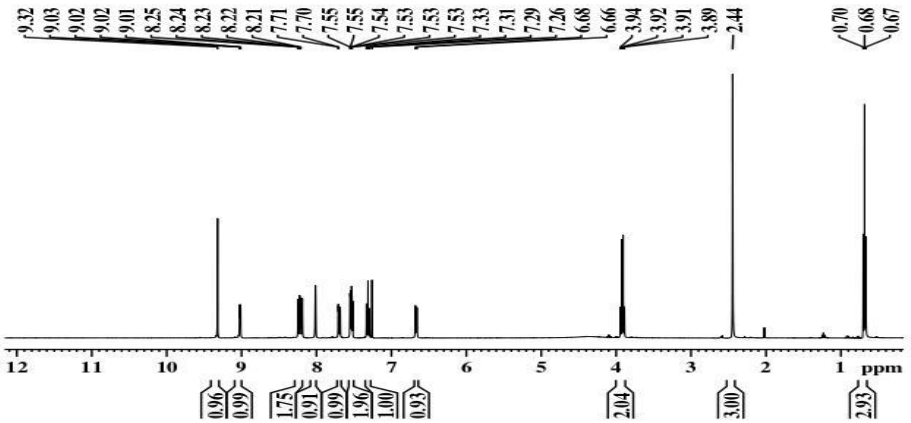


Fig. 5

Off white solid;yield: 73%; mp: 270-280 oC; 1H NMR (400 MHz, CDCl3) δ 9.332 (1H), 9.02 (1H),8.23 (2H), 7.70 (1H), 7.55 (1H), 7.53 (2H), 7.30 (1H), 6.87 (1H), 3.92 (2H), 2.44 (3H, p-Toluidine),0.68 (3H, CH3).

^{13}C NMR of ethyl 6-methyl-4-(naphthalen-8-yloxy)quinoline-3-carboxylate.

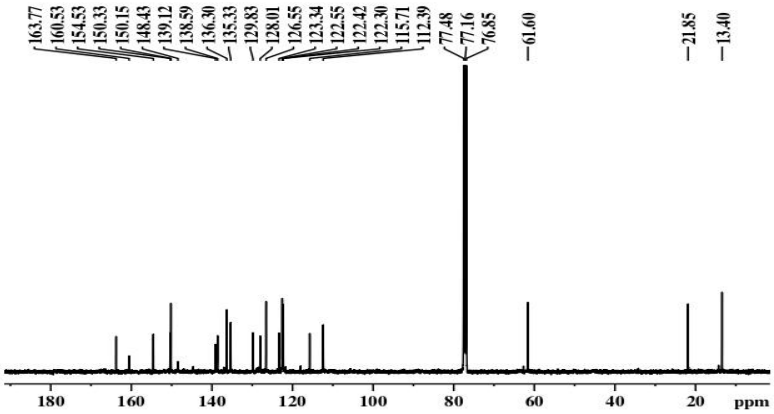


Fig. 6

13C NMR (100 MHz, CDCl3) δ 163.77, 160.53, 154.53, 150.33, 150.15, 148.43, 139.12, 138.59,136.30, 135.33, 129.83, 128.01, 126.55, 123.34, 122.55, 122.42, 122.30, 115.71, 112.39, 61.60,21.85, 13.40.

HRMS of ethyl 6-methyl-4-(naphthalen-8-yloxy)quinoline-3-carboxylate

Fig. 7

HRMS(TOF) Calcd. for C22H18N2O3Na [M+Na]+, 381.1215; found, 381.1215.

IX. CONCLUSION

- Quinoline based compounds were designed and synthesized via feasible synthetic route.
- Compounds were designed and docked with ParDOCK, IIT Delhi.
- The binding free energy value of the synthesized compound i.e. A docked with *Pf*PMT is -8.74kcal/mol.

The synthesized compounds were characterized with different spectroscopic techniques i.e. ^{1}HNMR, ^{13}CNMR and HRMS.

REFERENCES

[1.] Wotodjo, A.N.; Trape, J. F.; Richard, V.; Doucouré, S.; Diagne, N.; Tall, A.; Ndiath, O.; Faye, N.; Gaudart, J.; Rogier, C.; Sokhna, C. *PLoS One*, **2015**, 10
[2.] Vangapandu, S.; Jain, M.; Kaur, K.; Patil, P.; Patel, S. R.; Jain, R. *Med. Res. Rev*. **2007**, 27 (1), 65-107
[3.] Volkman, S. K.; Barry, A. E.; Lyons, E. J.; Nielsen, K. M.; Thomas, S. M.; Choi, M. Thakore, S. S.; Day, K. P.; Wirth, D. F.; Hartl, D. L. *Science*. **2001**, 293 (5529), 482-484
[4.] Caraballo, H.; King, K. *Emergency Medicine Practice*. **2014** 16 (5), 1-23.
[5.] Urban, B.C.; Ing, R.; Stevenson, M. M. *Immunology and Immunopathogenesis of Malaria*.**2005**, 297, 25-70
[6.] Poinar, G. *Syst. Parasitol*. **2005**, 61 (1), 47-52
[7.] Beeson, J. G.; Boeuf, P.; Fowkes, F. J. *BMC Med*. **2015**, 13 (1), 110
[8.] Eastman, R. T.; Fidlock, D. A. *Nat. Rev. Microbiol*. **2009**, 7 (12) 864-874
[9.] Cox, F. E. Parasite Vectors, **2010**, 3 (1), 5
[10.] Gupta, V.; Mittal, M.; Sharma, V. *Oman Med. J*. **2014**, 29 (2), 142-145
[11.] Burrows, J. N.; Leroy, D.; Lotharius, J.; Waterson, D.; Challenges in antimalarial drug discovery. *Future Med. Chem*. **2011**, 3 (11), 1401-1412
[12.] Sherman, I. W. (1998). A Brief History of Malaria and Discovery of the Parasite's Life Cycle. Chapter 1 of Malaria: Parasite Biology, Pathogenesis and Protection. Edited by Sherman IW, ASM Press
[13.] Baker, D. A. Malaria gametocytogenesis. *Mol. Biochem. Parasitol*. **2010**, 172 (2), 57-65
[14.] Frevert, U. *Trends Parasitol*. **2004**, 20 (9), 417-424
[15.] Mitamura, T.; Hanada, K.; Ko-Mitemura, E. P.; Nishijima, M.; Horii, T. *Parasitol. Int*. **2000**, 49(3), 219-229. Wang, R.; Charoenvit, Y.; Daly, T. M.; Long, C. A.; Corradin, G.; Hoffman, S. L. *Immunol. Lett*. **1996**, 53 (2–3), 83-93
[16.] J. Wiesner et al. / Bioorg. Med. Chem. Lett. 11 (2001) 423±424
[17.] S. M. Jones et al. / Bioorg. Med. Chem. 12 (2004) 683–692
[18.] Chem. Soc. Rev., 2010, 39, 435–454
[19.] College of Pharmacy, Institute of Pharmaceutical Research and Development, Wonkwang University, 460, Iksan-daero, Iksan, Jeolabuk-do 54538, Republic of Korea