European Journal of Medicinal Chemistry 45 (2010) 1583–1589

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and *in vitro* microbiological evaluation of an array of biolabile 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides

V. Kanagarajan, J. Thanusu, M. Gopalakrishnan*

Synthetic Organic Chemistry Laboratory, Department of Chemistry, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India

ARTICLE INFO

Article history:
Received 29 June 2009
Received in revised form
22 December 2009
Accepted 29 December 2009
Available online 14 January 2010

Keywords:
2-Amino-4,6-diarylpyrimidines
Morpholine
Acetamide
Chloroacetyl chloride
Antibacterial activity
Antifungal activity

ABSTRACT

Biolabile 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **34**–**42** have been synthesized and evaluated for their *in vitro* antibacterial and antifungal activities. The minimum inhibitory concentration tested for the same compounds against the same set of bacterial and fungal strains shows that the compounds **36** and **38** against *β-Heamolytic streptococcus* and *Klebsiella pneumonia*, **40** against *Escherichia coli* and *Pseudomonas*, have excellent antibacterial activity. Compounds **36**, **38** and **42** show inhibition against *Aspergillus flavus*, compound **41** against *Microsporum gypsuem*, **42** against *Mucor*, and compounds **39** and **40** against *Rhizopus*.

1. Introduction

Now-a-days, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Among the nitrogen containing heterocyclic compounds, pyrimidines apparently gained considerable importance owing to their varied biological properties and therapeutical importance. Pyrimidines are the basic nucleus in nucleic acids and have been associated with a number of biological activities. Substituted aminopyrimidine nuclei are common in marketed drugs such as anti-atherosclerotic aronixil®, anti-histaminic thonzylamine®, anti-anxielytic buspirone®, anti-psoriatic enazadrem®, and other medicinally relevant compounds. Some notable biological activity of pyrimidine derivatives includes adenosine receptor antagonists [1], kinase inhibitors [2], analgesic [3], anti-inflammatory [3], inhibitors of cyclin-dependent kinases 1 and 2 [4], calcium channel antagonist [5], anti-histaminic [6], antitubercular [7] activities.

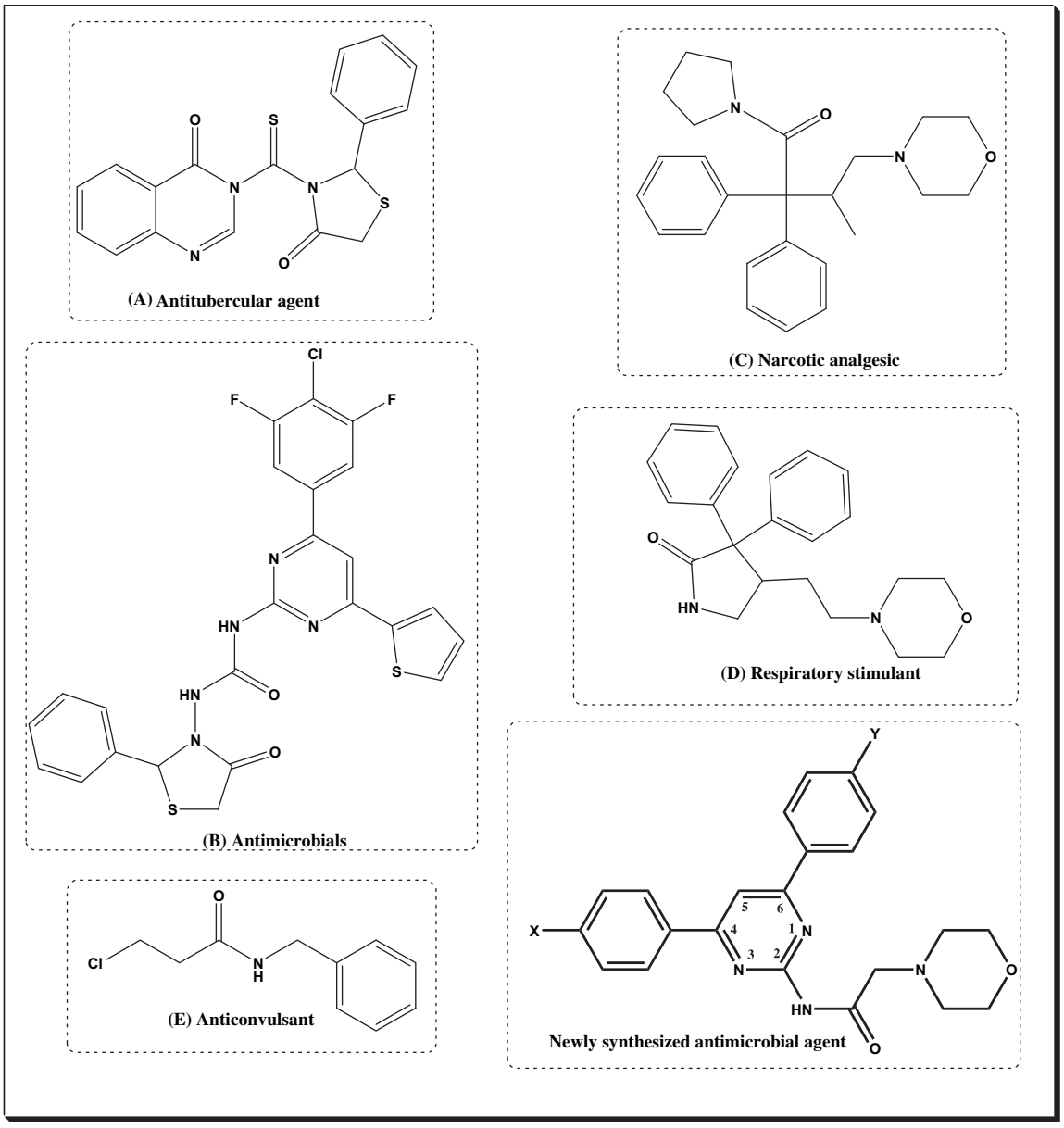
Promising diverse pharmacological activities were shown by various N-fuctionalized morpholines. They were reported to exert a number of important physiological activities such as antidiabetic [8], antiemetic [9], platelet aggregation inhibitors, anti-hyperlipoproteinemics [8] bronchodilators, growth stimulants [10] and antidepressants [11]. These were also used in the treatment of inflammatory diseases, pain, migraine and asthma [12]. Tridemorph®, a morpholine derivative was used as an antifungal agent [13]. 4-Phenyl morpholine derivatives were reported to possess anti-inflammatory [14] and central nervous system [15] activities. Besides these, amides are well known for their therapeutic values. The chemistry of amides having a chloroacetyl group was also very fascinating and has received significant attention now-a-days. *N*-Benzyl-β-chloropropionamide was a well-proven anticonvulsant agent [16]. Moreover, synthesis and *in vitro* antimicrobial activity of a new heterocyclic compounds which contain both morpholine and pyrimidine moiety together namely 4-(4-morpholinophenyl)-6-arylpyrimidin-2-amines were reported [17].

It was known from Scheme 1 that some clinically useful compounds containing pyrimidines moiety exhibit strong tuberculosis (A) and antimicrobial activity (B). Besides, some of the clinically important drugs contain morpholine moiety in addition to N-heterocycles which are separated by one or higher number of carbon atoms. Drugs derived from morpholine incorporated compounds include dextromoramide®, (C) a narcotic analgesic and doxapram HCl, (D) a respiratory stimulant. Doxapram® was used in the treatment of respiratory depression following anaesthesia. *N*-Benzyl-β-chloropropionamide (E) was a very good anticonvulsant and was marketed under the trade name Hibicon® and Hydrane®.

Recently, we exploited the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [18], 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones [19], 6-aryl-1,2,4,5-tetrazinane-3-thiones [20], 2,6-

* Corresponding author. Tel.: +91 4144 228 233.
E-mail address: profmgk@yahoo.co.in (M. Gopalakrishnan).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.12.068



Scheme 1. Some of the synthetic compounds having the core pyrimidine, acetamide and morpholine nuclei with therapeutic activities.

diarylpiperidin-4-one derivatives [21-23] with a view to incorporate various other bioactive heterocyclic nucleus such as 1,2,3-selenadiazoles, 1,2,3-thiadiazoles, diazepans intact for evaluation of associated antibacterial and antifungal activities. Commercially available drugs have either pyrimidine or morpholine moiety only. In continuation of our earlier work on the synthesis of various structurally diverse heterocyclic compounds, we thought it was worthwhile to synthesize compounds comprising all pyrimidines, chloroacetyl amides and morpholine moiety together to furnish a compact structure like title 2-morpholino-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **34**–**42** with the hope to develop some promising antimicrobial agents.

2. Results and discussion

2.1. Chemistry

The Claisen–Schmidt condensation of equimolar quantities of appropriate acetophenone and appropriate benzaldehyde in the presence of sodium hydroxide yielded *E*-1,3-diarylprop-2-en-1-ones **7**–**15**. When *E*-1,3-diarylprop-2-en-1-ones **7**–**15** were refluxed with guanidine nitrate in the presence of sodium hydroxide, 2-amino-4,6-diarylpyrimidines **16**–**24** were formed. Various substituted 2-chloro-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **25**–**33** were synthesized by electrophilic substitution reaction of chloroacetyl chloride with the corresponding parent 2-amino-4,6-diarylpyrimidines **16**–**24** in the presence of triethylamine as base and toluene as solvent. Besides using sodium carbonate/potassium carbonate as a base and toluene as solvent, appreciable yields were obtained when triethylamine was used as a base and toluene as solvent to effect chloroacetylation of 2-amino-4,6-diarylpyrimidines at ambient temperature. In addition, while using stronger bases as sodium hydroxide, potassium hydroxide and pyridine individually to effect chloroacetylation, undesired products were obtained along with the expected product. The physical and analytical data for compounds **7**–**33** was given in Table 1. Then, condensation of 2-chloro-*N*-(4,6-diarylpyrimidin-2-yl)acetamides **25**–**33** with morpholine in the presence of anhydrous potassium