Chinese Chemical Letters 27 (2016) 707–710

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis, antimicrobial and anti-inflammatory activities of some novel 5-substituted imidazolone analogs

Ashwani Kumar Dhingra [a,b,*], Bhawna Chopra [a,b], Rameshwar Dass [c], Sanjeev Kumar Mittal [d]

[a] Guru Gobind Singh College of Pharmacy, Yamuna Nagar 135001, Haryana, India
[b] Department of Pharmacy, IK Gujral Punjab Technical University, Jalandhar 144001, Punjab, India
[c] Department of Industrial Chemistry, Guru Nanak Khalsa College, Yamuna Nagar 135001, Haryana, India
[d] IEC School of Pharmacy, IEC University, Baddi 173205, Himachal Pardesh, India

ARTICLE INFO

Article history:
Received 18 June 2015
Received in revised form 14 December 2015
Accepted 18 January 2016
Available online 6 February 2016

Keywords:
Oxazolones
Imidazolones
Antimicrobial activity
Anti-inflammatory activity

ABSTRACT

In view of potent antimicrobial and anti-inflammatory activities exhibited by 5-substituted imidazolones, a variety of novel imidazolone analogs **3a-l** were synthesized by the condensation of different substituted oxazolones **1** with various aromatic amines **2.** All the synthesized compounds were screened for *in vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. Several analogs produced good or moderate activities particularly against the tested Gram-positive bacteria *Micrococcus luteus a*nd Gram-negative bacteria *Pseudomonas aeruginosa* and. Meanwhile, compounds **3b** and **3c** displayed marked antifungal activity against *C. albicans*. In addition, the *in vivo* anti-inflammatory activity of the synthesized compounds was determined using the carrageenin-induced paw oedema method in rats. Two of 5-substituted imidazolone derivatives, **3k** and **3d** show good anti-inflammatory activity. The structures of all the newly synthesized compounds were elucidated using IR, ^{1}H NMR and ^{13}C NMR.

1. Introduction

At present, diverse classes of compounds posses anti-inflammatory activity including non-steroidal anti-inflammatory drugs (NSAIDS), steroidal anti-inflammatory agents or synthetic forms of natural cortisol (glucocorticoids), pharmaceutical biologics and many more. Although the drug treatment has been improved to steadily but yet, it is still a challenge for the pharmaceutical chemists to identify more effective, potent, less toxic therapeutic agents to treat as well as reduce the signs and symptoms of acute inflammation and chronic inflammatory diseases. In addition, it is well known that bacterial infections often produce pain and inflammation. In normal practice, two groups of agents (chemotherapeutic and anti-inflammatory) are prescribed simultaneously to treat bacterial infections with inflammatory disorders. Unfortunately, none of the drugs possesses these three activities in a single component. Therefore, our aim is to find a compound having dual antimicrobial and anti-inflammatory activities. Here, we are presenting some 5- substituted imidazolone analogs with comparable antibacterial and anti-inflammatory potencies.

5-Imidazolone is a five-membered heterocyclic ring system having three carbon and two nitrogen atoms at the 1 and 3 positions with a carbonyl group at the 5 position. Several imidazolone analogs were also found to be associated with diverse biological activities including analgesic and anti-inflammatory [1–4], CNS depressant [5], monoamine oxidase (MAO) inhibitory [6], anticonvulsant [6,7], immunomodulator [8], antianthelmintic [9], anticancer [10], cardiovascular [11,12], antimicrobial [13,14] *etc.* Previously the imidazolones have been prepared by heating a mixture of 5-oxazolones derivatives with aromatic and substituted aromatic amine in the presence of pyridine for 10–15 h. The yield of imidazolones was very poor and the reaction required a long time [15–19]. In this report we have introduced some new imidazolone analogs, synthesized by the condensation of 5-oxazolones analogs with substituted aromatic amines in the presence of anhydrous pyridine under microwave irradiation.

* Corresponding author at: Punjab Technical University, Research Scholar, Department of Pharmacy, Guru Gobind Singh College of Pharmacy, Yamuna Nagar-135001, Haryana, India.
E-mail address: ashwani1683@gmail.com (A.K. Dhingra).

http://dx.doi.org/10.1016/j.cclet.2016.01.049

The structures of all the prepared analogs were determined using IR, ^{1}H NMR and all the prepared analogs were screened for antimicrobial and anti-inflammatory potential.

2. Experimental

2.1. Chemistry

All melting points were determined by the open capillary tube method and are uncorrected. IR spectra were recorded on a Perkin Elmer RX1 spectrophotometer using KBr pellets and are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer in ($CDCl_3$) using TMS as an internal reference and chemical shifts were measured in δ ppm. The progress of the reaction was monitored by TLCanalysis using 0.2 mm thickness aluminum sheets pre-coated with silica gel Merck 60F 254 and visualization was done using iodine/UV lamp. The solvents were removed under reduced pressure using a Buchi rotary evaporator.

2.2. General procedure for the synthesis of title compounds **3a-l**

A series of 5-substituted imidazolones were synthesized by the condensation of different 5-substituted oxazolones (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine under solvent free conditions in a microwave reactor (Scheme 1). The reaction was completed in 10–15 min. The completion of reaction was monitored by TLC analysis and then 5 mL of ice-cooled 5% HCl in water was added and the mixture was left for overnight. The resultant solids were collected and washed with water. The resultant solid was crystallized from ethanol, filtered and dried to afford titled compounds **3a-l**.

4-(3-Nitrobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3a**: Yield: 70%. Mp 214–216 °C; IR (KBr, cm^{-1}): 1615 (C=N), 1597 (C=C), 1645 (C=O). ^{1}H NMR ($CDCl_3$, 100 MHz): δ 7.25 (s, 1H), 6.90–8.25 (m, 12H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170, 158.4, 148, 136.2, 132.4, 130.2, 128.5, 121, 117, 108.

4-(3-Nitrobenzylidene)-1-(3-nitrophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3b**: Yield: 72%. Mp 217–219 °C; IR (KBr, cm^{-1}): 1620 (C=N), 1598 (C=C), 1655 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (s, 1H), 7.31–8.54 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170, 164.4, 147, 136, 133.2, 132.5, 130, 129.5, 128, 126, 121,116, 106.

4-(3-Nitrobenzylidene)-1-(naphthalen-1-yl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3c**: Yield: 67%. Mp 223–224 °C; IR (KBr, cm^{-1}): 1605 (C=N), 1590 (C=C), 1660 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (s, 1H), 6.80–8.25 (m, 16H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 164.1, 148.2, 141.2, 136.5, 134.2, 132.5, 130.0, 128.4, 126.2, 124.4, 121.2, 119.0, 109.3, 108.4.

4-(2-Chlorobenzylidene)-2-phenyl-1-(pyridin-2-yl)-1*H*-imidazol-5(4*H*)-one **3d**: Yield: 77%. Mp 216–217 °C; IR (KBr, cm^{-1}): 1610 (C=N), 1594 (C=C), 1655 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.7 (s, 1H), 6.80–8.10 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 164.3, 147.5, 138.2, 133.1, 131.2, 130.4, 128.3, 126.2, 113.4, 109.5, 108.3.

4-(2-Chlorobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3e**: Yield: 79%. Mp 210–212 °C; IR (KBr, cm^{-1}): 1600 (C=N), 1580 (C=C), 1650 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.8 (s, 1H), 6.80–7.70 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 164.0, 158.3, 133.2, 131.2, 129.4, 128.5, 128.2, 126.5, 126.2, 123.3, 121.0, 117.1, 108.2.

4-(4-Fluorobenzylidene)-2-phenyl-1-(pyridin-2-yl)-1*H*-imidazol-5(4*H*)-one **3f**: Yield: 76%. Mp 238–240 °C; IR (KBr, cm^{-1}): 1610 (C=N), 1596 (C=C), 1645 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.6 (s, 1H), 6.70–8.10 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 164.3, 162.2, 148.1, 138.2, 130.6, 130.2, 128.4, 128.0, 126.1, 115.4, 113.1, 109.2, 108.1.

4-(4-Fluorobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3g**: Yield: 68%. Mp 228–230 °C; IR (KBr, cm^{-1}): 1620 (C=N), 1595 (C=C), 1650 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.7 (s, 1H), 6.90–7.60 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 164.3, 162.3, 158.4, 130.4, 129.6, 128.5, 128.2, 126.1, 123.4, 121.0, 117.1, 115.4, 108.3.

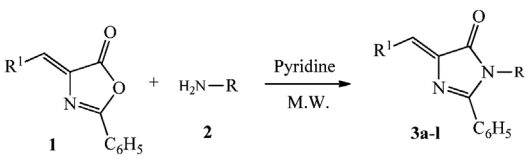
4-(4-Fluorobenzylidene)-1-(2,6-dimethylphenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3h**: Yield: 60%. Mp 238–239 °C; IR (KBr, cm^{-1}): 1618 (C=N), 1590 (C=C), 1645 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.3 (s, 6H), 7.6 (s, 1H), 6.80–7.60 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 164.2, 162.3, 142.3, 134.2, 130.4, 128.6, 128.0, 126.3, 124.4, 115.2, 108.1.

4-(4-Hydroxybenzylidene)-2-phenyl-1-(pyridin-2-yl)-1*H*-imidazol-5(4*H*)-one **3i**: Yield: 62%. Mp 234–235 °C; IR (KBr, cm^{-1}): 1620 (C=N), 1590 (C=C), 1650 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.0 (s, 1H), 7.6 (s, 1H), 6.70–8.10 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 164.2, 157.3, 147.4, 138.3, 130.2, 128.6, 127.0, 126.3, 115.2, 113.1, 109.2, 108.4.

4-(4-Hydroxybenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3j**: Yield: 64%. Mp 242–243 °C; IR (KBr, cm^{-1}): 1610 (C=N), 1592 (C=C), 1655 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.0 (s, 1H), 7.6 (s, 1H), 6.70–7.80 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 164.2, 157.2, 130.2, 128.6, 127.3, 126.1, 123.4, 121.3, 117.4, 115.4, 108.1.

4-(4-Methoxybenzylidene)-2-phenyl-1-(pyridin-2-yl)-1*H*-imidazol-5(4*H*)-one **3k**: Yield: 70%. Mp 235–237 °C; IR (KBr): 3105 (Ar C–H), 1620 (C=N), 1594 (C=C), 1645 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (s, 3H), 7.5 (s, 1H), 6.70–8.10 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 164.1, 159.2, 147.5, 138.3, 130.0, 128.3, 127.4, 126.1, 114.2, 113.4, 109.4, 108.1, 55.1.

4-(4-Methoxybenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1*H*-imidazol-5(4*H*)-one **3l**: Yield: 72%. Mp 225–227 °C; IR (KBr, cm^{-1}): 3100 (Ar C-H), 1615 (C=N), 1590 (C=C), 1660 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (s, 3H), 7.6 (s, 1H), 6.70–7.70 (m, 12H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.1, 164.1, 159.4, 158.4, 130.2, 128.4, 127.2, 126.1, 123.4, 121.0, 117.2, 114.4, 108.1, 55.2.



3a: R= 3- Cl, 4-F-phenyl, R^1= 3-NO_2-phenyl
3b: R=R^1= 3-NO_2-phenyl
3c: R= Napthyl, R^1= 3-NO_2-phenyl
3d: R= Pyridyl, R^1= 2-Cl-phenyl
3e: R=3- Cl, 4-F-phenyl, R^1= 2-Cl-phenyl
3f: R= Pyridyl, R^1= 4-F-phenyl
3g: R= - Cl, 4-F-phenyl, R^1=4-F-phenyl
3h: R= 2, 5-dimethylbenzene, R^1=4-F-phenyl
3i: R= Pyridyl, R^1= 4-OH-phenyl
3j: R= 3- Cl, 4-F-phenyl, R^1= 4-OH-phenyl
3k: R= Pyridyl, R^1= *p*-methoxybenzene
3l: R= 3- Cl, 4-F-phenyl, R^1= *p*-methoxybenzene

Scheme 1. Preparation of 5-substitituted imidazolones.

2.3. Biological activity

2.3.1. Antimicrobial activity

The *in vitro* antimicrobial potential of all the prepared analogs was carried out at Institute of Microbial Technology (CSIR), Chandigarh-160036 (India) using the agar plate diffusion antimicrobial bioassay. The compounds were tested at 5000 μg/mL