Synthesis of new morpholine-connected pyrazolidine derivatives and their antimicrobial, antioxidant, and cytotoxic activities

Radhakrishnan Surendra Kumar, Meera Moydeen, Salem S. Al-Deyab, Aseer Manilal, Akbar Idhayadhulla

PII: S0960-894X(16)31175-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.11.032
Reference: BMCL 24427

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 18 June 2016
Revised Date: 16 October 2016
Accepted Date: 12 November 2016

Please cite this article as: Surendra Kumar, R., Moydeen, M., Al-Deyab, S.S., Manilal, A., Idhayadhulla, A., Synthesis of new morpholine-connected pyrazolidine derivatives and their antimicrobial, antioxidant, and cytotoxic activities, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.11.032

ELSEVIER

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Synthesis of new morpholine-connected pyrazolidine derivatives and their antimicrobial, antioxidant, and cytotoxic activities

Radhakrishnan Surendra Kumar[a], Meera Moydeen[b] , Salem S. Al-Deyab[b] , Aseer Manilal[c], and Akbar Idhayadhulla [a,*]

[a] P.G. & Research Department of Chemistry, Nehru Memorial College, Puthanampatti 621007, Tiruchirappalli (Dt), Tamil Nadu, India
[b] Petrochemical Research Chair, Department of Chemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
[c] Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Arba Minch University, Arba Minch, Ethiopia

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
morpholine-connected pyrazolidine
pyrrolidine metal-free catalysis
antimicrobial activity
antioxidant activity
cytotoxic activity

ABSTRACT[1]

A simple and convenient one-pot four-component synthesis of morpholine-connected pyrazolidine derivatives **2a–f** and **4a–f** was developed using direct metal-free catalysis, with the identities of the synthesized compounds confirmed by IR, NMR (^{1}H and ^{13}C), mass spectrometry, and elemental analysis. The prepared compounds were inspected for antimicrobial, antioxidant, and cytotoxic activities.

Antimicrobial and antifungal activities against five bacterial and four fungal pathogens, respectively, were investigated using the disc diffusion technique. In antibacterial activity, compounds **2d** and **2f** (MIC = 2 µg/mL) exhibited significantly higher activity than the standard ciprofloxacin. The results of antifungal assay showed that the activity of compound **4a** (MIC = 0.5 µg/mL) was significantly higher than the standard clotrimazole. Antioxidant activity was screened based on $ABTS^{\bullet+}$ radical scavenging and linoleic acid peroxidation performance. Compound **4a** showed substantial antioxidant (91.3%) activities, as compared with the Trolox standard. Cytotoxicity was evaluated using HepG2 (liver), HeLa (cervical), and MCF-7 (breast) cancer cell lines, with high toxicities observed for **2b** (GI_{50} = 12.2 µm) and **4a** (GI_{50} = 07.8 µm).

The pyrazolidine structural motif is present in several compounds exhibiting significant anti-inflammatory, antidepressant, anticancer, antibacterial, and antiviral activities,[1–7] while morpholine derivatives possess substantial anticancer[8] and antifungal[9] activities, with morpholino-triazenes inhibiting cytochrome P450 1A1 and 1B1.[10] Some representative examples of bioactive morpholine and pyrazolidine derivatives are shown in Figure 1.

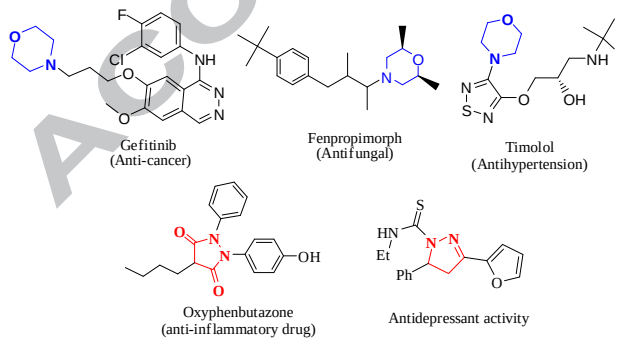
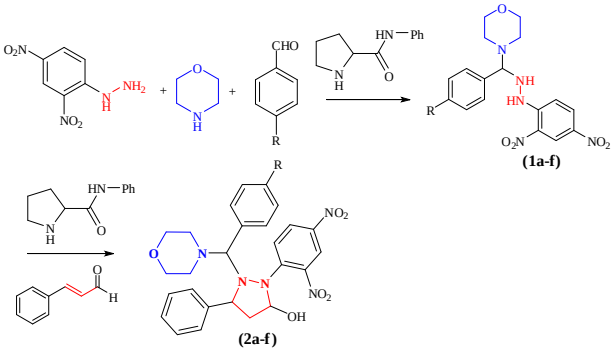


Figure 1. Selected biologically active morpholine and pyrazolidine derivatives.

Pyrazolidines can be synthesized using both metal and metal-free catalysis,[11] with their asymmetric synthesis requiring catalysis by chiral amines.[12]

During our studies, an elegant report appeared on the direct metal-free catalytic synthesis of pyrazolidine derivatives based on this strategy (Scheme 1),[13] also describing the screening for anticancer, antimicrobial, and antioxidant activities.



R= -Ph(**1a, 2a**), -Ph-Cl(**1b, 2b**), -Ph-OH(**1c, 2c**), -Ph-NO_2(**1d, 2d**), -Ph-OCH_3(**1e, 2e**), -Ph-$N(CH_3)_2$ (**1f, 2f**)

Scheme 1. Synthesis of compounds **2a-f**.

In the first step, benzaldehyde (0.1 mol) was reacted with morpholine (0.1 mol) and 2,4-dinitrophenylhydrazine (0.1 mol) in the presence of a chiral pyrrolidine-based catalyst in ethanol to furnish compounds **1a–f**. In the second step, these compounds

* Corresponding author. Tel.: +91 9994265115;
E-mail address: a.idhayadhulla@gmail.com; idhayadhulla@nmc.ac.in