Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 120 (2014) 176–184

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Synthesis, spectral characterization, self-assembly and biological studies of *N*-acyl-2-pyrazolines bearing long alkoxy side chains

Asghar Abbas [a,*], Habiba Nazir [b], Muhammad Moazzam Naseer [a,*], Michael Bolte [c], Safdar Hussain [d], Noureen Hafeez [e], Aurangzeb Hasan [a,f]

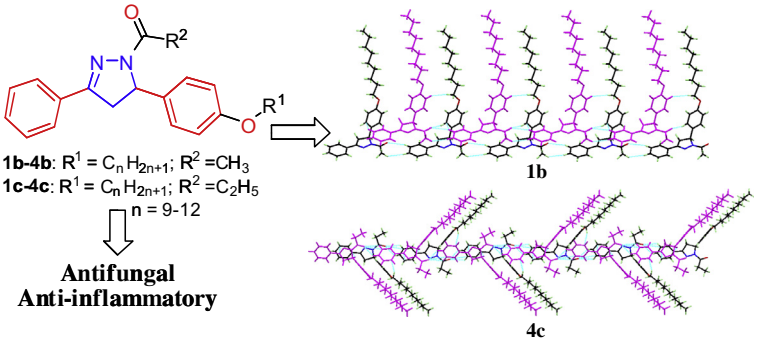
[a] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
[b] Department of Biochemistry, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
[c] Institut fur Anorganische Chemie, J.W. Goethe-Universitat Frankfurt, Max-von-Laue-Str. 7, 60438 Frankfurt/Main, Germany
[d] Department of Forensic Medicine & Toxicology, National University of Science and Technology, Islamabad 44000, Pakistan
[e] Department of Forensic Medicine & Toxicology, IIMC, Riphah International University Islamabad, Pakistan
[f] Department of Chemistry, Faculty of Science, University of Malaya, Kuala Lumpur 50603, Malaysia

HIGHLIGHTS

- Pyrazolines are attractive drug scaffold with many biological applications.
- Synthesis of new pyrazoline derivatives equipped with *N*-acyl arms and long alkoxy side chains.
- Spectral, self-assembly, antifungal and anti-inflammatory studies.
- Effect of alkoxy chain length on molecular packing and bioactivity.

GRAPHICAL ABSTRACT

A series of new pyrazoline derivatives equipped with *N*-acyl arms and long alkoxy groups as side chains was synthesized to investigate the effect of alkoxy chain length on molecular packing and bioactivity.



ARTICLE INFO

Article history:
Received 2 September 2013
Received in revised form 30 September 2013
Accepted 2 October 2013
Available online 14 October 2013

Keywords:
Pyrazolines
Spectral characterization
Self assembly
Antifungal
Anti-inflammatory

ABSTRACT

A series of new pyrazoline derivatives (**1b–4c**) bearing *N*-acyl arms and nine to twelve carbon long alkoxy side chains was synthesized and characterized on the basis of spectroscopic data and microanalysis. The nature of self-assembly to understand the interplay of alkoxy chain crystallization and various supramolecular interactions was investigated using single crystal X-ray diffraction studies. Interesting self-assembled supramolecular structures of **1b** and **4c** were observed in the crystal lattice owing to various CH···O, H···H, CH···π, lonepair···π and π···π interactions. Further, all the synthesized compounds (**1b–4c**) were screened for their *in vitro* antifungal and anti-inflammatory activities. Compounds **2b**, **3b**, **2c** and **3c** showed significant to moderate antifungal activity against *Microsporum canis* whereas most of the other compounds were found inactive against all the five tested fungal strains. Good anti-inflammatory activity was observed for compounds **1b** with IC_{50} value 331 μM compared to 273 μM for Indomethacine, a standard reference drug. The bio-activity data demonstrates the relationship between lipophilicity, solubility and bioavailability.

Introduction

Diversely substituted pyrazolines embedded with variety of functional groups represent a class of compounds of immense

* Corresponding authors. Tel.: +92 333 5009600; fax: +92 51 90642241.
E-mail addresses: profazmi@hotmail.com (A. Abbas), moazzam@qau.edu.pk (M.M. Naseer).

1386-1425/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2013.10.023

importance in heterocyclic chemistry [1–6]. Pyrazoline ring is a dihydropyrazole having two adjacent nitrogen atoms and one endocyclic double bond. Considerable amount of research activity has been directed towards this class by the medicinal chemists. Among all its isomers, 2-pyrazoline has gained more attention due to its broad spectrum biological properties [7–9] and its presence in a number of pharmacologically important molecules such as azolid/tandearil (anti-inflammatory), phenazone/amidopyrene/methampyrone (analgesic and antipyretic), anturane (uricosuric) and indoxacarb (insecticidal). Therefore, a number of pharmacological activities [7–9] are documented in recent years for this class of compounds and still it is an active area of research [10–15].

The properties of solids are often governed by the way in which their constituent molecules are packed [16–23]. Therefore, understanding of the molecular packing is crucial in crystal engineering and structural chemistry to deliberately engineer the solid state materials of desired properties and functions. Both intra- and intermolecular interactions, such as hydrogen bonding, Van der Waals interaction, CH···π and π···π stacking play an important role in controlling the self-assembly of molecules in the crystal lattice [24–32]. However, the knowledge of intermolecular forces that hold the molecules in the solid state is still inadequate, offering a big challenge to the crystal engineers and supramolecular chemist's community to fully understand molecular packing and to predetermine the self-assembly processes and properties of solids [33–36].

The interaction of drugs with biological systems depends on the ability of a particular drug to penetrate various biological membranes, tissues and barriers. Both lipophilicity of drug as physicochemical parameter and composition of microbial membranes play an important role in the permeation of a drug through the microbial membranes for further drug action [37,38]. Owing to their structural diversity, easy access and tremendous importance, a series of new pyrazoline derivatives equipped with *N*-acyl arms and long alkoxy groups as side chains were chosen to investigate the effect of alkoxy chain length on molecular packing and bioactivity. The molecules were designed to understand the significance of the interplay of weak interactions and the role of alkoxy side chain toward the self-assembly in the solid state. Effect of alkoxy chains on antifungal and anti-inflammatory activities of the synthesized compounds was also investigated. The compounds of the present series as potential chelating agents may be good future candidates for the design of metal-based therapeutic agents with improved bioactivities.

Experimental

Materials and methods

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as required. Thin layer chromatography (TLC) was performed using aluminum sheets (Merck) coated with silica gel 60 F_{254}. Elemental analyses were carried out with a CHNS Analyzer, Model LECO-183. ^{1}H and ^{13}C NMR spectra of compounds were recorded with a Bruker 300 MHz spectrometer using deuterated solvents and TMS as internal standard. IR spectra of compounds were recorded on a Bio-Rad FTS 3000 MX spectrophotometer (400–4000 cm^{-1}). The melting points of compounds were determined using capillary tubes and an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo, Japan. *In vitro* anti-inflammatory and antifungal properties were studied at Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical Sciences, University of Karachi, Pakistan.

*General procedure for the synthesis of compounds **(1a–4c)***

The compounds (**1a**–**4c**) were synthesized following the previously reported procedure [39]. The carboxylic acid solution (25 ml) of the respective 4-alkoxychalcone (0.01 mol) containing a few drops of hydrochloric acid was heated at 60–65 °C for 30 min with constant stirring. Hydrazaine hydrate (80%) (1.0 g, 0.02 mol) was then added dropwise to the reaction flask. After complete addition, the reaction mixture was heated to reflux for another 4–5 h. The reaction mixture was then cooled to room temperature and poured onto the crushed ice. The precipitates thus formed, were filtered, washed with distilled water and dried. The crude products were further purified by silica gel column chromatography using petroleum ether/ethyl acetate (4:1) as the mobile phase.

*1-Acetyl-3-phenyl-5-(4-nonyloxyphenyl)-2-pyrazoline **(1b)***

Yield 85%; yellowish white crystals; m.p. 78–81 °C; R_f = 0.69 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1677 (s), 1648 (s), 1499 (s), 1295 (m), 1254 (s), 1050 (m), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.2 Hz, —O—$(CH_2)_8$—C***H***$_3$), 1.29–1.50 (m 12H, —O—CH_2—CH_2—(C***H***$_2$)$_6$—CH_3), 1.77 (qn 2H, J = 7.8 Hz, —O—CH_2—C***H***$_2$—C_7H_{15}), 2.43 (s, 3H, O=C—C***H***$_3$), 3.18 (dd, 1H, J = 4.8, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, J = 12.0, 17.7 Hz, ***H***$_b$), 3.92 (t, 2H, J = 6.6 Hz, —O—C***H***$_2$—), 5.57 (dd, 1H, J = 4.5, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, J = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, J = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',\ g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.6, 26.0, 29.1, 29.2, 29.3, 29.5, 31.8, 42.3, 59.4, 68.0, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\cdot}$ 406, Base Peak 363). Anal. calcd. for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89; Found: C, 76.77; H, 8.39; N, 6.96%.

*1-Acetyl-3-phenyl-5-(4-decyloxyphenyl)-2-pyrazoline **(2b)***

Yield 87%; yellowish white crystals; m.p. 81–83 °C; R_f = 0.71 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1685 (s), 1637 (s), 1497 (s), 1293 (m), 1252 (s), 1049 (m), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz, —O—$(CH_2)_9$—C***H***$_3$), 1.29–1.50 (m 14H, —O—CH_2—CH_2—(C***H***$_2$)$_7$—CH_3), 1.77 (qn 2H, J = 7.0 Hz, —O—CH_2—C***H***$_2$—C_8H_{17}), 2.43 (s, 3H, O=C—C***H***$_3$), 3.18 (dd, 1H, J = 4.5, 17.4 Hz, ***H***$_a$), 3.74 (dd, 1H, J = 12.0, 17.7 Hz, ***H***$_b$), 3.93 (t, 2H, J = 6.6 Hz, —O—C***H***$_2$—), 5.57 (dd, 1H, J = 4.5, 11.7 Hz, ***H***$_x$), 6.84 (d, 2H, J = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, J = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.47 (m, 3H, Ar$H_{f=f',\ g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.6, 26.0, 29.2, 29.3, 29.3, 29.5, 29.5, 31.9, 42.2, 59.4, 68.0, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\cdot}$ 420, Base Peak 377). Anal. calcd. for $C_{27}H_{36}N_2O_2$: C, 77.10; H, 8.63; N, 6.66; Found: C, 77.03; H, 8.57; N, 6.73%.

*1-Acetyl-3-phenyl-5-(4-undecyloxyphenyl)-2-pyrazoline **(3b)***

Yield 88%; yellowish white crystals; m.p. 80–82 °C; R_f = 0.68 (petroleum ether:ethyl acetate, 4:1), FT-IR (KBr, cm^{-1}) 1683 (s), 1639 (s), 1495 (s), 1298 (m), 1251 (s), 1047 (m), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz, —O—$(CH_2)_{10}$—C***H***$_3$), 1.28–1.50 (m 16H, —O—CH_2—CH_2—(C***H***$_2$)$_8$—CH_3), 1.76 (qn 2H, J = 7.8 Hz, —O—CH_2—C***H***$_2$—C_9H_{19}), 2.43 (s, 3H, O=C—C***H***$_3$), 3.18 (dd, 1H, J = 4.5, 17.7 Hz, ***H***$_a$), 3.74 (dd, 1H, J = 11.7, 17.7 Hz, ***H***$_b$), 3.92 (t, 2H, J = 6.6 Hz, —O—C***H***$_2$—), 5.57 (dd, 1H, J = 4.5, 11.7 Hz, ***H***$_x$), 6.85 (d, 2H, J = 8.7 Hz, Ar$H_{c=c'}$), 7.17 (d, 2H, J = 8.7 Hz, Ar$H_{d=d'}$), 7.44–7.48 (m, 3H, Ar$H_{f=f',\ g}$), 7.75–7.79 (m, 2H, Ar$H_{e=e'}$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.0, 22.7, 26.0, 29.1, 29.2, 29.3, 29.3, 29.5, 29.6, 31.9, 42.2, 59.4, 68.0, 114.7 (2C), 126.5 (2C), 126.9 (2C), 128.7 (2C), 130.2, 131.5, 133.8, 153.8, 158.6, 168.8, (EI) *m/z* ($M^{+\cdot}$ 434, Base Peak