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ORIGINAL ARTICLE

Synthesis, antioxidant and analgesic activities of Schiff bases of 4-amino-1,2,4-triazole derivatives containing a pyrazole moiety

Synthèse, activités anti-oxydantes et analgésiques de bases de Schiff dérivées du 4-amino-1,2,4-triazole porteur d'un noyau pyrazole

K. Karrouchi[a,c,*], **L. Chemlal**[b], **J. Taoufik**[a], **Y. Cherrah**[b], **S. Radi**[c], **M. El Abbes Faouzi**[b], **M. Ansar**[a]

[a] *Laboratory of Medicinal Chemistry, Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco*
[b] *Laboratory of Pharmacology and Toxicology, Pharmacokinetic Research Team, Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco*
[c] *LCAE, Department of Chemistry, Faculty of Sciences, University Mohamed I, Oujda, Morocco*

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Summary A series of Schiff bases of 4-amino-1,2,4-triazole derivatives containing pyrazole (**5a—h**) were synthesized from condensation of 4-amino-5-(5-methyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol (**3**) derivative with various aromatic aldehydes (**4a—h**). The structures of the synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. All the synthesized compounds (**5a—h**) were screened for their in vivo analgesic and in vitro antioxidant activities revealing significant analgesic and antioxidant properties.

* Corresponding author. Laboratory of Medicinal Chemistry, Faculty of Medicine and Pharmacy, University Mohammed V, Rabat, Morocco.
E-mail address: Khalid.karrouchi@um5s.net.ma (K. Karrouchi).

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MOTS CLÉS
1,2,4-Triazole ;
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Résumé Une série de bases de Schiff dérivées du 4-amino-1,2,4-triazole porteur d'un noyau pyrazole (**5a—h**) ont été synthétisées par condensation de 4-amino-5-(5-méthyl-1*H*-pyrazol-3-yl)-*4H*-1,2,4-triazole-3-thiol (**3**) et de divers aldéhydes aromatiques **(4a—h)**. Les structures des composés synthétisés (**5a—h**) ont été élucidées par IR, RMN ^{1}H, RMN ^{13}C et la spectrométrie de masse. Tous les composés synthétisés ont été criblés pour leur activité analgésique in vivo et anti-oxydante in vitro. Les résultats ont montré des activités analgésique et anti-oxydante significatives.

Introduction

Pyrazole derivatives are important biologically active heterocyclic compounds. These derivatives are the subject of many studies due to their widespread biological activities, such as anti-inflammatory [1,2], antioxidant [3], antipyretic [4], antimicrobial [5—7], antiviral [8], anticancer [9,10], anticonvulsant [11], analgesic [12], antidepressant [13], insecticide and fungicide [14,15].

Compounds with the structure of azomethine group (—C=N—) are known as schiff bases, which are usually synthesized from the condensation of primary amines and compounds having active carbonyl groups. Further, Schiff bases represent an important class of organic compounds, especially in the medicinal and pharmaceutical fields. The chemistry of Schiff bases derived from 1,2,4-triazole analogues has been an interesting field of study for a long time. It is well known from the literature that Schiff bases derived from 1,2,4-triazole displayed excellent biological properties. In particular, they show antibacterial, antifungal [16], antitubercular [17], antioxidant [18], antitumor [19,20], analgesic [21], anti-inflammatory [22] and pesticidal properties [23,24]. They are important molecules in the medicinal and pharmaceutical fields and it has been suggested that the azomethine linkage might be responsible for their biological activities.

The goal of this study was to synthesize and evaluate biological properties of some Schiff bases of 4-amino-1,2,4-triazoles carrying pyrazole moiety (Scheme 1) as antioxidants and analgesic agents.

Results and discussions

Chemistry

The main goal of the present study was to synthesize and investigate the antioxidant and analgesic activities of Schiff base analogous of 1,2,4-triazoles carrying a pyrazole moiety. Synthesis of the intermediate and target compounds was performed according to the reactions outlined in Scheme 1.

The starting compound 5-methyl-1*H*-pyrazole-3-carbohydrazide (**1**) was prepared following a previously reported literature procedure [25]. Intermediate triazole (**3**) was synthesized from corresponding hydrazide (**1**) through multi-step reactions as per the reported literature [26]. The hydrazide (**1**) was treated with carbon disulfide and potassium hydroxide in ethanol at room temperature; it afforded the corresponding potassium salt **(2)** in 84% yield. Treatment of the potassium salt (**2**) with hydrazine hydrate in refluxing ethanol afforded a single product identified as 4-amino-5-(5-methyl-1*H*-pyrazol-3-yl)-*4H*-1,2,*4*-triazole-3-thiol (**3**) in 67% yield. The structure of 4-amino-5-(5-methyl-1*H*-pyrazol-3-yl)-*4H*-1,2,*4*-triazole-3-thiol (**3**) was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometries. IR spectrum of the latter product revealed absorption bands at 3367, 3144, and 2732 cm^{-1} characteristic for NH, NH_2 and SH groups, respectively. The ^{1}H NMR spectrum showed the down field broad singlet at δ 2.26 ppm for the CH_3 protons. This compound also showed prominent singlets at δ 13.20 and δ 13.75 ppm for its NH and SH protons, respectively. A singlet at δ 6.63 ppm was also seen for its CH-pyrazole protons. The ^{13}C NMR spectrum showed characteristic signals at 10.69 (CH_3), δ 105.08 (C4-pyrazole), and 138.64, 139.90, 155.40 and 165.06 (C=O), thereby accounting for the presence of six different carbon atoms in the molecule. Further, mass spectrum showed a (M+1) peak at *m/z* 197.0 corresponding to its molecular formula, $C_6H_8N_6S$.

The synthesis of different Schiff base derivatives of compounds **(5a—h)** was carried out by the reaction of compound (**3**) with various substituted aromatic aldehydes (**4a—h)** in the presence of catalytic amount of acetic acid under refluxing ethanol. The ^{1}H, ^{13}C NMR spectra of compounds **(5a—h)** displayed additional signals, while the signal of —NH_2 group of the 4-amino-1,2,*4*-triazole structure disappeared. The IR spectrum of the compound 4-(benzylideneamino)-5-(5-methyl-1*H*-pyrazol-3-yl)-*4H*-1,2,4-triazole-3-thiol **(3a)** showed the absence of —NH_2 stretching band, thus indicating the Schiff base formation. The other characteristic stretching vibrations of the product were 3115 cm^{-1} (N—H), 1605 cm^{-1} (C=N). The ^{1}H NMR spectrum showed prominent singlets at δ 2.24 ppm for its CH_3 protons. Two characteristic singlets at δ 6.46 and δ 9.43 ppm were due to C—H and N=CH protons of the pyrazole ring and of the azomethine group, respectively. The five protons of phenyl moiety appeared as multiplet at δ 7.53—7.92 ppm. The ^{13}C NMR spectrum of compound showed signals at δ 10.65 (CH_3), 105.34, 129.33, 129.65, 132.48, 133.30, 138.34, 140.00, 144.88, 162.47 and 168.58. The mass spectrum showed a protonated molecular ion (M+1) peak at *m/z* 285.1, consistent with its molecular formula $C_{13}H_{12}N_6S$. The structure and reaction yields of the compounds **(5a—h)** are provided in Table 1.