European Journal of Medicinal Chemistry 46 (2011) 5317–5326

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles

V. Padmavathi*, C. Prema kumari, B.C. Venkatesh, A. Padmaja

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 24 May 2011
Received in revised form
20 August 2011
Accepted 23 August 2011
Available online 29 August 2011

Keywords:
Pyrroles
Pyrazoles
Oxazoles
Thiazoles
Imidazoles
Antimicrobial activity

ABSTRACT

A new class of amido linked bis heterocycles *viz*., pyrrolyl/pyrazolyl-oxazoles, thiazoles and imidazoles were prepared by 1,3-dipolar cycloaddition of TosMIC and diazomethane to the respective cinnamamide derivatives and screened for antimicrobial activity. The chlorosubstituted imidazolyl cinnamamide (6c) is the most potential antimicrobial agent as it displayed strong antibacterial activity against *Bacillus subtilis* and antifungal activity against *Penicillium chrysogenum*.

1. Introduction

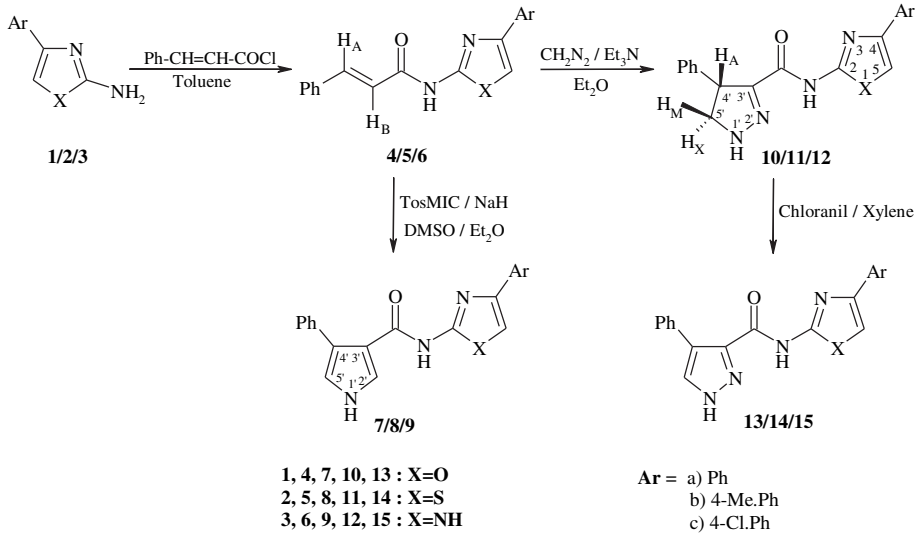
Azoles constitute immensely important members of the aromatic heterocycle family due to their presence in a myriad of bioactive natural products as privileged pharmacophores. The pyrrole motif attracts particular attention in methodology design for its utility as a synthetic building block and widespread occurrence in target structures, such as functional materials and biologically-relevant compounds [1–5]. Among the highly marketed COX-2 inhibitors that comprise the pyrazole nucleus, celecoxib is the one which is treated as a safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocyclic template that is known to selectively inhibit the COX-2 enzyme. Some other examples of pyrazole derivatives as NSAIDs are mefobutazone, ramifenazone, famprofazone [6–9]. The oxazole ring is endowed with various activities such as hypoglycemic [10], analgesic [11], anti-inflammatory [12] and antibacterial. Besides, oxazoles showed antiproliferative activity against many cancer cells, especially human prostate cancer and human epidermoid carcinoma [13–15]. The thiazolyl group is also of great importance as it appears frequently in the structures of various natural products and biologically active compounds like thiamine (vitamin-B) and also in some antibiotic drugs like penicillin, micrococcin [16] and many metabolic products of fungi and primitive marine animals etc. In recent years, the high therapeutic properties of the imidazole related drugs have been attracting the attention of medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Medicinal properties of imidazole containing compounds include anticancer [17], antimicrobial [18–21] and antioxidant [22]. It is known that clinically useful drugs such as miconazole, econazole and oxiconazole having imidazole moiety exhibit strong antifungal activity. In fact, polyamides composed of *N*-methylpyrrole, *N*-methylimidazole and large varieties of analogous five membered heteroaromatic amino acids have been designed with predictable sequence selectivity and many of these designed polyamides bind in the DNA minor groove with high affinities [23–25]. Motivated by the aforesaid findings and pursing our studies on different five membered heterocycles [26], we were designed to synthesize a new series of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles and tested them as antimicrobial agents.

2. Chemistry

The synthetic pathway that leads to the formation of the title compounds **7**-**15** are sketched in Scheme 1. By adopting the literature precedent 4-aryloxazol-2-amine (**1**), 4-arylthiazol-2-amine (**2**) and 4-aryl-1*H*-imidazol-2-amine (**3**) were prepared from the

* Corresponding author. Tel.: +91 877 2289303; fax: +91 877 2261825.
E-mail address: vkpuram2001@yahoo.com (V. Padmavathi).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.08.032



Scheme 1. Pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles.

synthetic intermediate, phenacyl bromide [27,28]. Aromatic heterocyclic styrylamides, (*E*)-*N*-(4-aryloxazol-2-yl)cinnamamide (**4**), (*E*)-*N*-(4-arylthiazol-2-yl)cinnamamide (**5**) and (*E*)-*N*-(4-aryl-1*H*-imidazol-2-yl)cinnamamide (**6**) were prepared by the reaction of **1**, **2** and **3** with cinnamoyl chloride (Scheme 1). The ^{1}H NMR spectra of **4a**, **5a** and **6a** showed a singlet at δ 7.60, 7.50 and 7.52 due to C_5—H and another broad singlet at 8.35, 8.28 and 8.21 ppm due to NH. The **6a** also showed a broad singlet at 11.20 due to NH of imidazole ring. The signals of NH disappeared on deuteration. In addition, two doublets were observed at δ 7.88, 7.81, 7.75 and 6.71, 6.43, 6.39 ppm which were assigned to olefin protons, H_A and H_B, respectively. The coupling constant value J_{AB} ~16.0 Hz indicated that they are in *trans* geometry. The olefin moiety present in these compounds was used to develop pyrrole [29] and pyrazole [30] units. Thus treatment of **4**, **5** and **6** with tosylmethyl isocyanide in the presence of sodium hydride in a mixture of dimethyl sulfoxide and ether produced 4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**7**), 4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**8**) and 4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrrole-3′-carboxamide (**9**) (Scheme 1). The ^{1}H NMR spectra of **7a** displayed three singlets at δ 7.65, 6.82 7.10, **8a** at 7.74, 6.62, 6.68 and **9a** at 7.77, 6.58, 6.81 ppm due to C_5—H, $C_{2'}$—H and $C_{5'}$—H, respectively. Furthermore, two broad singlets were observed at δ 9.87, 9.81, 9.85 due to NH of pyrrole ring and at 8.23, 8.12, 8.25 due to CONH in these compounds. In addition, compound **9a** displayed a broad singlet at 11.46 due to NH of imidazole ring. Apart from these, the olefin moiety present in **4**, **5** and **6** was used to develop pyrazoline ring by 1,3-dipolar cycloaddition of diazomethane in ether in the presence of triethylamine at −20° to −15 °C for 42—48 h. The compounds 4′,5′-dihydro-4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**10**), 4′,5′-dihydro-4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**11**) and 4′,5′-dihydro-4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**12**) obtained were characterized by spectral parameters (Scheme 1). In the ^{1}H NMR spectra of **10a**, **11a** and **12a**, the methine and methylene protons of pyrazoline ring displayed an AMX splitting pattern. The three double doublets observed at δ 4.43, 4.02, 3.60 in **10a**, at 4.38, 4.21, 3.58 in **11a** and at 4.40, 4.11, 3.66 ppm in **12a** were assigned to H_A, H_M and H_X. The coupling constant values J_{AM} = 11.6, J_{AX} = 6.1, J_{MX} = 11.1 in **10a**, J_{AM} = 11.7, J_{AX} = 6.2, J_{MX} = 11.2 in **11a** and J_{AM} = 11.5, J_{AX} = 6.4, J_{MX} = 11.3 Hz in **12a** indicated that H_A, H_M are *cis*, H_A, H_X are *trans* while H_M, H_X are *geminal*. Apart from these, the C_5—H displayed a singlet at δ 7.65 in **10a**, at 7.72 in **11a** and at 7.68 ppm in **12a**. However, two broad singlets were observed at 8.98, 8.41 in **10a**, 8.81, 8.48 in **11a**, and 8.13, 8.02 in **12a** due to NH of pyrazoline and CONH, respectively which disappeared on deuteration. Aromatization of pyrazoline ring in **10**, **11** and **12** was effected by treating the latter compounds with chloranil in xylene to produce 4′-phenyl-*N*-(4-aryloxazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**13**), 4′-phenyl-*N*-(4-arylthiazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**14**) and 4′-phenyl-*N*-(4-aryl-1*H*-imidazol-2-yl)-1′*H*-pyrazole-3′-carboxamide (**15**). The ^{1}H NMR spectra of **13a** displayed two singlets at δ 7.60, 6.24, **14a** at 7.30, 6.31 and **15a** at 7.58, 6.12 ppm which were assigned for C_5—H and $C_{5'}$—H. Moreover, a broad singlet was observed at δ 6.61, 6.40 and 6.52 ppm in these compounds due to pyrazolyl NH which disappeared on deuteration. The structures of all the compounds were further ascertained by IR and ^{13}C NMR spectral data.

3. Antimicrobial activity

The results of antibacterial activity shown in Table 1 indicated that Gram-negative bacteria were more susceptible towards the tested compounds than Gram positive ones. When compared to the standard drug Chloramphenicol it was seen that **6c** and **15c** were effective particularly against *Pseudomonas aeruginosa* at 100 μg/ml. Amongst bis heterocyclic compounds, the aromatized bis heterocycles **13**, **14** and **15** were effective than the corresponding non-aromatized compounds **10**, **11** and **12**. Amongst pyrrole and pyrazole containing bis heterocycles, the latter compounds **13**, **14** and **15** displayed greater activity. The presence of chloro substituent on the aromatic ring enhances the activity (Fig. 1).

All the tested compounds inhibited the spore germination against tested fungi except the compound **10**. In general, most of the compounds showed slightly higher antifungal activity towards *Penicillium chrysogenum* than *Aspergillus niger*. The compounds **6c** and **15c** displayed excellent activity particularly against *P. chrysogenum* almost equivalent to the standard drug Ketoconazole (Table 2 and Fig. 2).

The MIC, MBC and MFC values of the compounds tested are listed in Table 3. The compound **6c** exhibited low MIC values when compared with **9c** and **15c**. In addition MBC value is 2×MIC in case of *Bacillus subtilis* and MFC value is 2×MIC in case of *P. chrysogenum*. However the other compounds showed the bactericidal and