Bioorganic & Medicinal Chemistry Letters 20 (2010) 5681–5685

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and evaluation of novel chloropyrrole molecules designed by molecular hybridization of common pharmacophores as potential antimicrobial agents

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ARTICLE INFO

Article history:
Received 25 March 2010
Revised 4 August 2010
Accepted 5 August 2010
Available online 10 August 2010

Keywords:
Chloropyrrole derivatives
1*H*-Pyrrole-2-carbohydrazide derivatives
Chalcones
Antimicrobial agents
Pyoluteorins

ABSTRACT

In an attempt to identify new potential lead as antimicrobial agent, 31 novel chloropyrrole derivatives of aroyl hydrazones and chalcones incorporating common pharmacophore of pyoluteorin derivatives were synthesized. Antimicrobial activity of the synthesized compounds was evaluated using broth dilution technique. Based on biological evaluation data it was observed that activity increases as the number of chlorines on pyrrole core increases. Few 1*H*-pyrrole-2-carbohydrazide derivatives shows activity equivalent to the standard drug ciprofloxacin. Thus, these compounds can act as potential lead for further antibacterial studies.

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. There is real perceived need for the discovery of new compounds endowed with antimicrobial activity, which are distinct from those of well-known classes of antibacterial agents to which many clinically relevant pathogens are now resistant.

Heterocycles containing pyrrole ring system are found to exhibit wide spectrum of biological activities and many of them show appreciable antibacterial,[1] antifungal,[2] antitumor[3], anticonvulsant,[4] anti-inflammatory agents,[5] and some are used as antibiotics.[6] For several decades, interest in pyrrole derivatives as antimicrobial agents has led to the preparation and antimicrobial evaluation of hundreds of such molecules.[7–9] Recently separated Celastramycin A, obtained from *Streptomyces* Mab-QuH-8 is known to be broad spectrum antibacterial agent.[10,11] Compounds related to Pyoluteorin have shown considerable activity against *Staphylococcus aureus*, *Shigella flexneri*, *Tricophyton asteroids*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris* and herbicidal activity.[12–16]

Hydrazones possessing an –CONHN=CH– azometine group constitute an important class of compounds for new drug development. Aroyl hydrazone derivatives have been demonstrated to possess, antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-malerial, antitubercular and antitumor activities.[17] These observations have been guiding for the development of new hydrazones that possess varied biological activities. Similarly chalcones have displayed an impressive array of biological properties among which antibacterial, antiprotozoal, anti-inflammatory, immunomodulatory, nitric oxide inhibition, tyrosinase inhibition, cytotoxic, anti-cancer, as well as antifungal and antitubercular activities have been cited in literature.[18]

On the basis of these literature reports we report synthesis and evaluation of a novel series of chloropyrrole derivatives designed by molecular hybridization of common pharmacophores of pyoluteorin derivatives (Fig. 1a) with aroyl hydrazones and chalcones. We have condensed the common 4,5-dichloro-2-acetylpyrrole moiety from each set of reported pyoluteorin derivatives with active pharmacophoric group of reported aroyl hydrazones and chalcones to get proposed hybrids. Yet another objective of the study was to evaluate the effect of chlorine atom/s on antimicrobial activity of pyrrole core and to optimize the activity through systematic modification of the substituent on the aromatic ring (Fig. 1b and c).

In the present work, 1*H*-pyrrole-2-carbohydrazide derivatives were synthesized utilizing the reaction sequence as shown in Scheme 1. Trichloroacetylation of pyrrole gave an excellent yield of **1**.[19] It was further converted in to ethyl ester which was chlorinated using sulfuryl chloride in ether to give ethyl-4-chloro-1*H*-pyrrole-2-carboxylate **3**.[20] 4,5-Dichoro-1*H*-pyrrole-2-carboxylate **5** was synthesized by using chlorine in acetic acid.[13] Esters were converted into corresponding hydrazides **6** which on condensation

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doi:10.1016/j.bmcl.2010.08.026

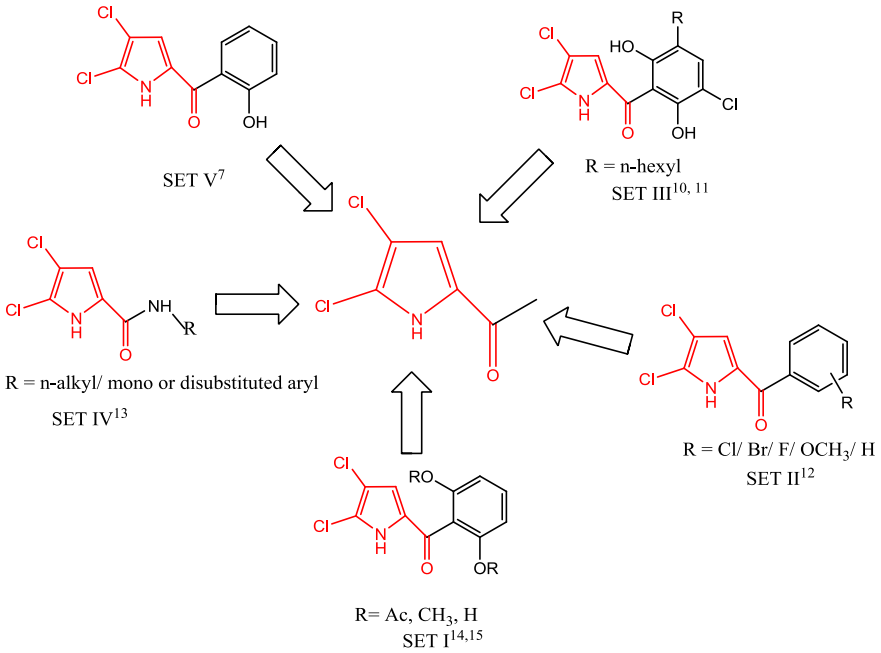


Figure 1a. Reported pyoluteorin derivatives as antimicrobial agents.

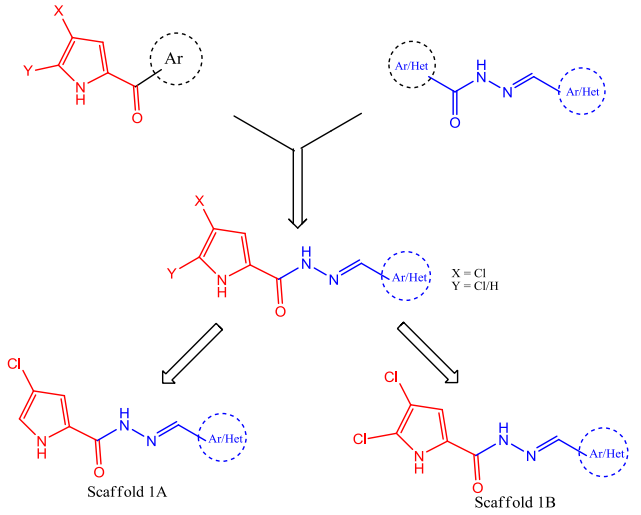


Figure 1b. Scaffold-1: Design of novel 4/4,5-dichloro-*N*′-arylidene-1*H*-pyrrole-2-carbohydrazide analogues using molecular hybridization approach.

with respective aldehydes gives 4/4,5-dichloro-*N*′-arylidene-1*H*-pyrrole-2-carbohydrazide analogues **7** and **12**.

2-Acetyl-1*H*-pyrrole was used as starting material for the synthesis of desired chloropyrrole chalcones derivatives (Scheme 2). 2-Acetyl-1*H*-pyrrole was chlorinated by sulfuryl chloride in ether to give corresponding 4/5/4,5-dichloro-2-acetylpyrroles **8**, **9**, and **10**.[21] Compounds **8**, **9**, and **10** were condensed with respective aldehydes to give chloropyrrole chalcone derivatives **11**.[22]

The Spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS) of all synthesized compounds were in agreement with the proposed structures. The newly prepared compounds were screened for their antibacterial activity against *E. coli* (ATCC-25922), *S. aureus* (ATCC-25923), *P. aeruginosa* (ATCC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method[23,24] and *Candida albicans* fungal strain in DMSO by agar dilution method.[27,28] The bacterial and fungal zones of inhibition values are given in Table 1. Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. The lowest concentration (highest dilution) required to arrest the growth of bacteria and fungi was regarded as minimum inhibitory concentration (MIC).[25–28] The minimum inhibitory concentrations are given in Table 1.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Compounds **12a**, **12b**, **12c**, **12d**, **12e**, **12f**, and **12i** showed good inhibition against *S. aureus* and *E. coli* species. Compounds **11k**, **11l**, **11m**, and **11n** exhibited good to moderate antibacterial activity. Especially compounds **12b**, **12d**, **12e**, **12f**, **12i**, and **11l** showed activity equivalent to standard against *S. aureus*. Antifungal activity screening study showed that among all the screened compounds **12a**, **12b**, **12c**, **12d**, **12e**, **12f**, **12h**, and **12i** showed good inhibition against *C. albicans*.

The chloro atom was found to be beneficial for the antimicrobial activity. The dichloro analogues were more active than corresponding monochloro analogues. These finding were analogues with the literature reports on different series where addition of second atom of halogen to the monochloro or mono bromo compound increased the activity while absence of halogen decreased activity.[29–31] Chlorinated derivatives were reported to be less active than brominated one.[9,30] Further development of this series with brominated compounds might be more effective. The number of chlorine atoms on pyrrole ring seems to be beneficial for activity. The reason may be attributed to the electron withdrawing nature of chlorine which will facilitate the interactions with probable active site and inhibits the growth of microbes. Aroyl hydrazones **12b**, **12c**, and **12e** were found to be more active than corresponding chalcones **11k**,

In summary, using systematic iteration of design, synthesis and evaluation, 31 new compounds based on the molecular hybridization of pyoluteorins with aroyl hydrazones and chalcones were synthesized and evaluated for their antimicrobial activity. Based on empirical structure–activity relationship data, it was observed that 4,5-dicloro-pyrroles derivatives are more active than 4-chloro/5-chloro-pyrroles. 5-Chloro-pyrrole derivatives are least active in corresponding series. 4,5-dichlor-2-pyrroyl hydrazones are more active than corresponding 4,5-dichloropyrrole chalcones. Molecules with furan moiety are more active than corresponding

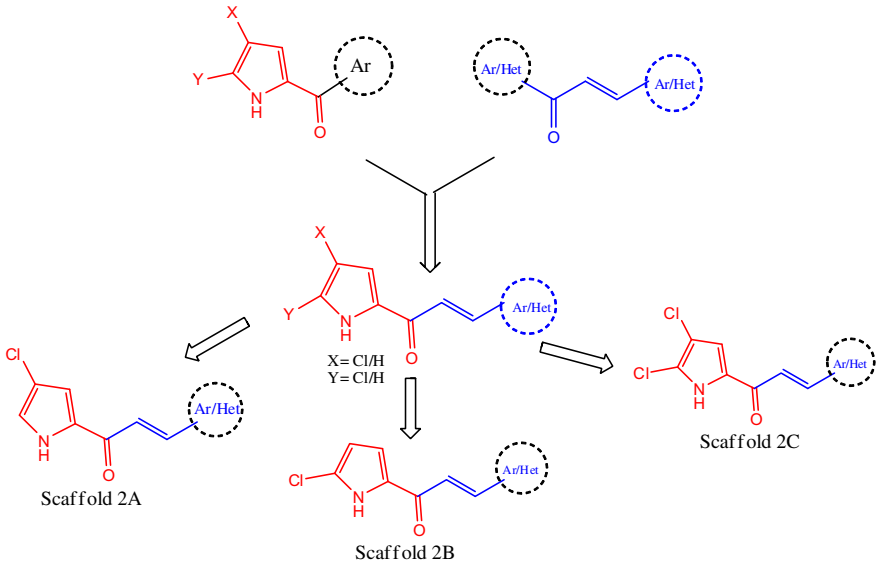
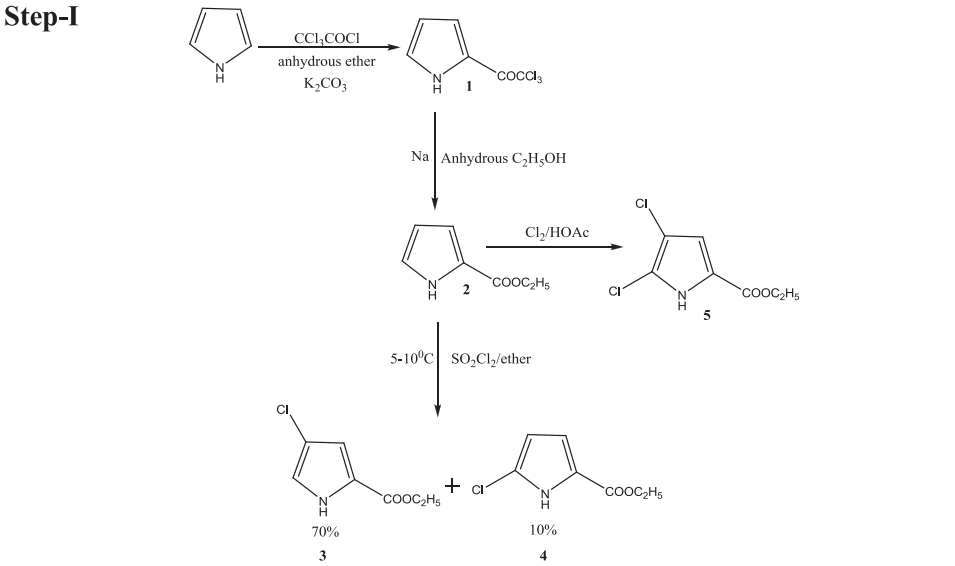
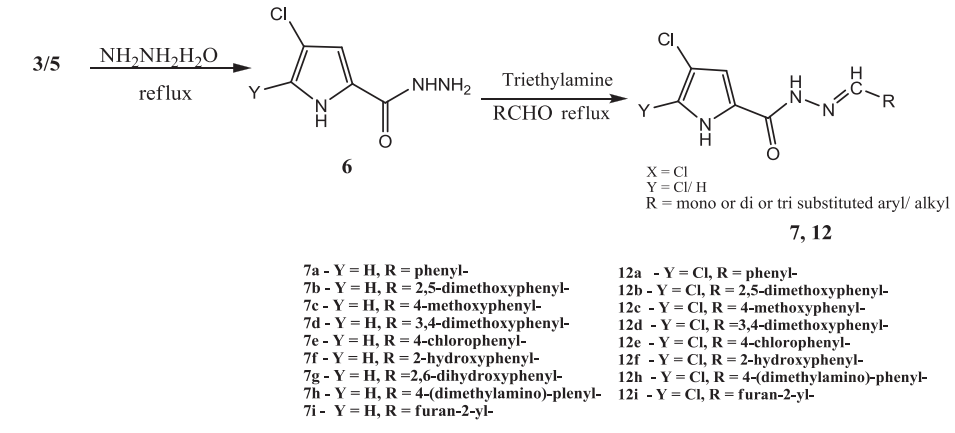
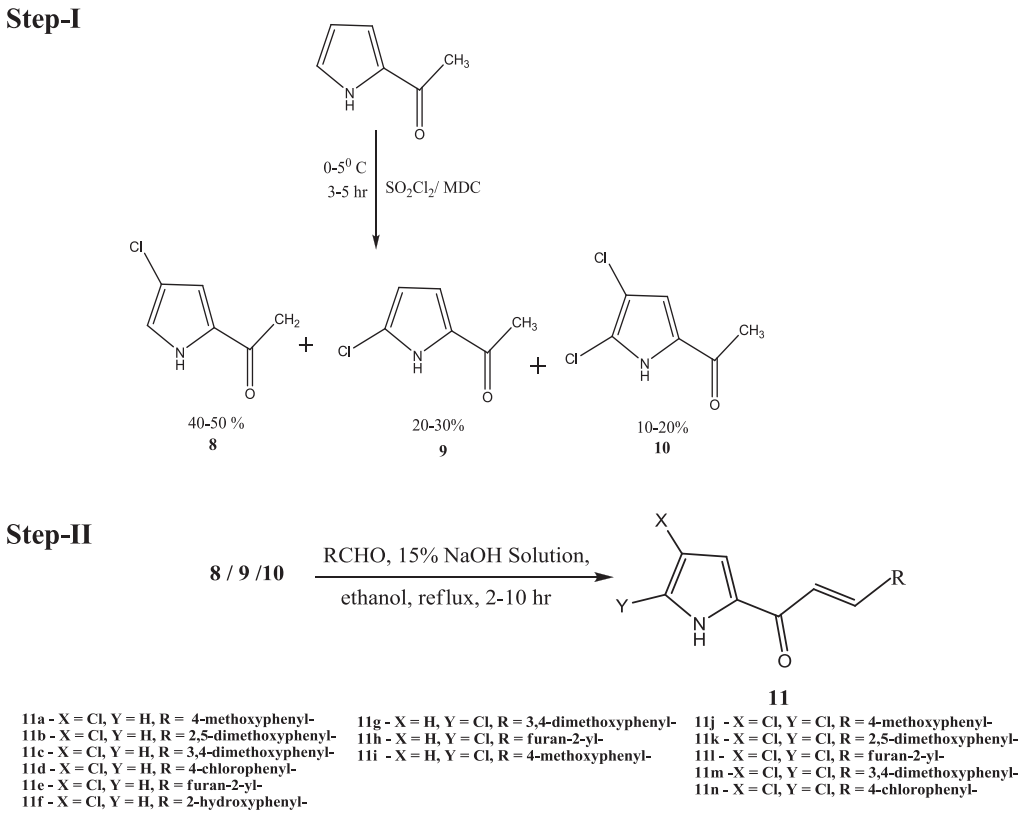


Figure 1c. Scaffold-2: Design of novel chloropyrrole chalcones using molecular hybridization approach.





Scheme 1. Synthesis of 4/4,5-dichloro-*N*′-arylidene-1*H*-pyrrole-2-carbohydrazide analogues.



Scheme 2. Synthesis of chloropyrrole chalcone anologues.

Table 1
Antimicrobial test results: (MIC μg/ml)

S. No.	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*C. abilcans*
7a	14(12.5)	17(12.5)	14(100)	—	20(25)
7b	15(12.5)	20(6.25)	15(100)	—	13(25)
7c	10(12.5)	18(12.5)	14(100)	—	15(25)
7d	12(12.5)	20(12.5)	16(100)	—	20(25)
7e	16(12.5)	26(3.125)	15(100)	—	17(25)
7f	20(6.25)	17(6.25)	14(100)	—	18(25)
7g	21(6.25)	24(3.12)	14(50)	—	18(25)
7h	17(12.5)	10(12.5)	14(100)	—	18(25)
7i	23(25)	24(25)	15(100)	—	21(25)
12a	11(12.5)	16(3.125)	18(50)	17(100)	23(12.5)
12b	20(3.125)	24(1.56)	13(25)	18(100)	24(12.5)
12c	19(12.5)	20(6.25)	20(25)	16(100)	24(12.5)
12d	20(3.125)	25(1.56)	18(12.5)	17(100)	24(12.5)
12e	22(3.125)	24(1.56)	16(25)	20(100)	20(12.5)
12f	18(3.125)	22(1.56)	18(50)	19(100)	16(12.5)
12h	22(6.25)	15(12.5)	15(25)	12(100)	22(12.5)
12i	24(3.125)	26(1.56)	24(25)	20(100)	23(12.5)
11a	16(12.5)	18(12.5)	15(25)	—	12(50)
11b	18(12.5)	19(12.5)	15(100)	—	16(50)
11c	16(12.5)	13(12.5)	14(100)	—	12(50)
11d	12(25)	16(12.5)	16(100)	—	13(50)
11e	20(12.5)	22(12.5)	17(25)	—	18(50)
11f	10(25)	16(12.5)	18(25)	—	15(50)
11g	13(25)	13(25)	—	—	14(100)
11h	16(12.5)	15(25)	—	—	10(100)
11i	10(50)	17(25)	—	—	14(100)
11j	13(12.5)	20(12.5)	17(100)	18(100)	12(50)
11k	20(6.25)	22(6.25)	15(100)	16(100)	15(50)
11l	21(3.125)	25(1.56)	17(25)	15(100)	14(50)
11m	15(6.25)	24(3.125)	17(25)	18(100)	18(50)
11n	16(6.25)	25(3.125)	16(25)	17(100)	14(50)
Standard[x]	25(1.06)	20(1.56)	25(3.125)	26(1.56)	25(1.56)

The representation '—' indicates that bacteria are resistant to the compounds, that is, >100 μg/ml. Diameter zone of inhibition is in millimeter. MIC values are given in brackets. MIC (μg/ml) = minimum inhibitory concentration, that is, lowest concentration to completely inhibit bacterial growth. X = (Standard) ciprofloxacin for antibacterial study and amphotericin B for antifungal study.

phenyl substituted moieties. Molecules with two chlorines in pyrrole ring were found to be more active than their monochloro substituted analogues. These analogues are more active on Gram positive bacteria than on Gram negative. Molecules show better activity on bacteria than on fungi. This molecular hybrid provides potential lead for further studies and development of antimicrobial molecules.

Acknowledgment

V.N.T. and R.A.R. acknowledge AICTE for financial support under Research Promotion Scheme.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.08.026.

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