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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of pyrrole-2-carboxamide derivatives: oroidin analogues

Balaram S. Takale · Neha V. Desai · Afsar Ali Siddiki · Hemchandra K. Chaudhari · Vikas N. Telvekar

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Abstract The reaction of pyrrole or dibromopyrrole-2-trichloroacetone with various amines results in the series of novel pyrrole-2-carboxamide bearing aromatic heterocycle or aryl or alkyl groups. Synthesized molecules were evaluated for their in vitro antibacterial activities. Most of the compounds exhibited potent activity against both Gram-positive and negative pathogens.

Keywords Antibacterial · Bromination · Carboxamides · Esters · Pyrrole

Introduction

The increased use of antibacterial and antifungal agents in recent years has resulted in the development of resistance to these drugs with significant implications for morbidity, mortality and health care costs (Kumar *et al.*, 2009). It is reported that certain infections that are essentially untreatable have begun to occur as epidemics both in the developing and other developed regions as a result of antimicrobial resistance (Rahangdale *et al.*, 2008. The infectious diseases are becoming a global problem since bacterial resistance has dramatically increased during the last two decades. Furthermore, antibacterial chemotherapy alone is ineffective to cure biofilm related infections, a major cause of nosocomial infections (Rice, 2006). Bacterial biofilm formation is often described as colonization of free floating bacteria on living or nonliving things (Costerton *et al.*, 1987; Hall-Stoodley *et al.*, 2004). Biofilm cause serious threat to individual who suffers from various diseases. Hence, there is a growing need for new classes of antibacterial agents able to address resistance and persistent infections because of biofilms (Imamura *et al.,* 2008; Lewis, 2001; Parsek and Singh, 2003).

The importance of Pyrrole unit especially in the biology is recently increasing, because of its presence in the natural products (Fresneda *et al.*, 2001; CosimaSchroif-Gregoire *et al.*, 2006). Various naturally occurring pyrrole alkaloids have been found to show antibiotic activity. Pyrrolomycin A and B (Ezaki *et al.,* 1981; Kaneda *et al.*, 1981) and the antibacterial Pyoluteorin (Bailey *et al.*, 1973) belong to class of pyrrole derivatives that since 1965, has been subjected to extensive structural modifications. Pyrrole-aminoimidazole alkaloids (PAIs) from marine sponges, including dibromosceptrin and oroidin **1c** (Walker *et al.*, 1981) show a broad spectrum of biological activities. The pyrrole moiety containing carboxamide is found to be an essential in the most cases for the antimicrobial activity, recently dihalo pyrrole carboxamides (Rane and Telvekar, 2010) were reported to be possess good antibacterial activity and also found to be important for the antimicrobial activity on the basis of biofilm formation (Ballard *et al.,* 2009).

In recent years, trans-cinnamic acid derivatives have attracted much attention due to their antimicrobial properties. Recently,the synergistic activity (Bezerra *et al.*, 2006) of trans-cinnamic acid in drug combinations with INH, rifamycin, and other known antimicrobial agents against *M. tuberculosis* has been exemplified. Importantly,

B. S. Takale · N. V. Desai · A. A. Siddiki · H. K. Chaudhari · V. N. Telvekar (✉)
Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Matunga, Mumbai 400 019, India
e-mail: vikastelvekar@rediffmail.com

superior intracellular and in vivo activity of a cinnamyl-rifamycin derivative in comparison with rifamycin (Rastogi *et al.,* 1998) was observed when tested against 20 susceptible and MDR *M. tuberculosis* strains. Significantly, trans-cinnamic acid was used to treat TB even before antimicrobial chemotherapy was used (Reddy *et al.,* 1995).

Molecular hybridization is recent concept where two pharmacophoric moieties of bioactive substance combine to give hybrid molecule with improved efficacy than parent compound (Viegas-Junior *et al.,* 2007). A series of novel molecules containing dibromopyrrole-2-carboxamides and cinnamic acid moiety were designed. Two moieties were combined with the help of ethane linkage. Other objective studied was the presence or absence of bromine or cinnamic acid in the compounds.

Chemistry

As we are continuously working on development of efficient routes for synthesis of organic molecules with interesting properties, we herein explored our previous methodology where we used insitu generated bromine for Decarboxylative bromination (Telvekar and Takale, 2011). Bromine generally used for the bromination is toxic and difficult to handle. Hence bromination with cheap and easily available reagent is need for this reaction; to support this we used Sodium nitrite in combination of aqueous HBr for bromination of pyrrole. In this case when we use liquid Br_2 product 2 obtained with 65 % yield.

We tried to use Catalytic $NaNO_2$ in the presence of air but rate of reaction was found to be very low. The respective product could be achieved in maximum yield when 2 equivalent of $NaNO_2$ was used (Table 1). When pyrrole-2-trichloracetone treated with 2 equivalent of $NaNO_2$ and 2 equivalents of 48 % aqueous HBr, the product 2 could be achieved in almost 85 % yield.

Experimental

General procedure for the bromination of 2-trichloroacetyl pyrrole

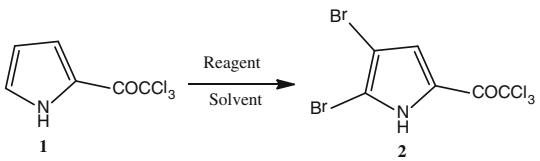
2-Trichloroacetyl pyrrole (2.6 mmol) and Sodium nitrite (5.2 mmol) were stirred in 10 ml of dichloromethane, 48 % aqueous HBr (5.2 mmol) was added dropwise through dropping funnel for period of 15 min. The reaction mixture was stirred for 4 h at room temperature and completion of reaction was monitored on TLC. Finally reaction mixture was diluted with 10 ml water and extracted with water. The organic layer was passed through dry Na_2SO_4 and evaporated using rotvac. The crude product was purified using silica gel column chromatography using hexane:ethylacetate (9/1) to give 85 % of pure dibromo product.

*Synthesis of dibromopyrrole-2-carboxamide from 4, 5-dibromopyrrol-2-yl trichloromethyl ketone (**3a–3f**)*

4,5-dibromopyrrol-2-yl trichloromethyl ketone 2 (1 mmol) and various aliphatic amines (1 mmol) were added to 10 ml of dichloromethane, the reaction mixture were stirred for 1–5 h after adding 4–5 drops of triethyl amine. Progress of the reaction was monitored on thin layer chromatography and after completion; the reaction mixture was diluted with dichloromethane and extracted with water. The organic layer was separated and evaporated to give crude product, which was purified by silica gel column chromatography with hexane:ethylacetate as eluent to get 60–85 % yield of pure product.

*N-benzyl-4,5-dibromo-1H-pyrrole-2-carboxamide **3a*** Brown solid; m.p. 255–258 °C; IR (KBr, cm^{-1}): 3335, 3195, 1610, 716; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.21 (s, 2H,

Table 1 Bromination of trichloroacetyl pyrrole



1 2

Entry	Reagent	Time (h)	Yield (%)
1	Br_2 (2 eq.)/$CHCl_3$/0 °C	8	60
2	Br_2 (2 eq.)/CH_2Cl_2/0 °C	6	65
3	$NaNO_2$ (2 eq.)/HBr (2 eq.)/CH_2Cl_2/RT	4	85
4	$NaNO_2$ (0.05 eq.)/HBr (2 eq.)/air/CH_2Cl_2/RT	24	10

–NH–CH_2–Ar), 6.12 (s, 1H, NH of pyrrole), 6.76 (s, 1H, CH of pyrrole), 7.21–7.42 (m, 5H, ArH), 11.23 (s, 1H, NH–C=O); ^{13}CNMR ($CDCl_3$, 400 MHz): δ 42.9 (ArCH$_2$–NH–), δ 127.5–101.0 (pyrrole), δ 138.7–127.1 (Ar–C), δ 161.2 (NH–C=O); MS *m/z*: 357.91(M^+), 359.91(M+2); Anal. calcd. for $C_{12}H_{10}Br_2N_2O$ (358.03): C, 40.26; H, 2.82; N, 7.82; Found: C, 40.12; H, 2.98; N, 7.90.

4,5-Dibromo-N-butyl-1H-pyrrole-2-carboxamide ***3b*** Brown solid; m.p. 230–232 °C; IR (KBr, cm^{-1}): 3341, 3161, 1609, 1568; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.81(t, 3H, –CH_2–CH_3), 1.27 (m, 2H,–CH_2–CH_3), 1.29–1.52 (m, 4H, –CH_2–CH_2–CH_3), 3.15 (q, 2H, CH_2–NH–), 6.12 (s, 1H, NH of pyrrole), 6.62 (s, 1H, CH of pyrrole), 11.12 (s, 1H, NH–C=O);^{13}C NMR ($CDCl_3$, 400 MHz): δ 12.7 (–CH_2–CH_3), δ 31.6 (–CH_2–)$_2$, δ 38.0 (CH_2–NH–), δ 128.1–99.7 (pyrrole), δ 160.3 (NH–C=O); MS *m/z*: 323.93(M^+), 325.93(M+2); Anal. calcd. for$C_{13}H_20Br_2N_2O$ (324.01): C, 41.08; H, 5.30; N, 7.37; Found: C, 41.21; H, 5.15; N, 7.30.

4,5-Dibromo-N-hexyl-1H-pyrrole-2-carboxamide ***3c*** Brown solid; m.p. 245–246 °C; IR (KBr, cm^{-1}): 3332, 3155, 1619, 1268; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, 3H, CH_2–CH_3), 1.28–1.35 (m, 6H,–CH_2–CH_2–CH_2–CH_3), 1.62 (m, 2H,–NH–CH_2–CH_2–CH_2–), 3.35 (t, 2H, CH_2–NH), 6.22 (s, 1H, NH fof pyrrole), 6.70 (s, 1H, CH of pyrrole), 11.01 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 13.3 (–CH_2–CH_3), δ 30.6–21.7 (–CH_2–)$_4$, δ 39.3 (CH_2–NH–), δ 128.1–99.7 (pyrrole), δ 160.3 (NH–C=O); MS *m/z*: 351.96(M^+), 353.96 (M+2); Anal. calcd. for$C_{11}H_{16}Br_2N_2O$ (352.07): C, 37.53; H, 4.58; N, 7.96; Found: C, 37.10; H, 4.70; N, 7.11.

4,5-Dibromo-N-(tert-butyl)-1H-pyrrole-2-carboxamide ***3d*** Brown solid; m.p. 240–241 °C; IR (KBr, cm^{-1}): 3351, 3175, 1611, 1233; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H,((–CH_3)$_3$), 6.32 (s, 1H, NH of pyrrole), 6.75 (s, 1H, CH of pyrrole), 11.05 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 13.3 (–CH_2–CH_3), δ 28.7 (–CH_3)$_3$, δ 61.2 (–C–NH–), δ 129.3–100.2 (pyrrole), δ 160.0 (NH–C=O); MS *m/z*: 323.93(M^+), 325.92 (M+2); Anal. calcd. for $C_9H_{12}Br_2N_2O$ (324.01): C, 33.36; H, 3.73; N, 8.65; Found: C, 33.15; H, 3.97; N, 8.74.

4,5-Dibromo-N-(1-phenylethyl)-1H-pyrrole-2-carboxamide ***3e*** Brown solid; m.p. 250–252 °C; IR (KBr, cm^{-1}): 3417, 3151, 1645, 1509;[1] H NMR ($CDCl_3$, 400 MHz): δ 1.62 (d, 3H, –CH–CH_3), 5.40 (m, 1H, CH_3(CH)Ph), 6.07 (d, 1H, NH of pyrrole), 6.60 (s, 1H, CH of pyrrole), 7.28–7.39(m, 5H, ArH), 11.27(s, 1H, NH–C=O);^{13}C NMR ($CDCl_3$, 400 MHz): δ 21.73 (ArCH–CH_3), δ 48.9(ArCH–NH–), δ 128.8–99.52(pyrrole), δ 142.62–126.03 (ArC), δ 158.82 (NH–C=O); MS *m/z*: 370.91(M^+), 373.52(M+2); Anal. calcd. for $C_{13}H_{12}Br_2N_2O$ (372.06): C, 41.97; H, 3.25; N, 7.53; Found: C, 42.03; H, 3.17; N, 7.59.

4,5-Dibromo-N-cyclohexyl-1H-pyrrole-2-carboxamide ***3f*** Brown solid; m.p. 249–250 °C; IR (KBr, cm^{-1}): 3418, 3115, 2927, 1647; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (m, 4H, –CH_2–CH_2–CH_2–CH_2– CH_2– of cyclohexane), 1.47 (m, 2H, –CH_2–CH_2–CH_2– of cyclohexane), 1.50 (m, 4H, (–CH_2)$_2$–CH–NH– of cyclohexane), 3.62 (m, 1H, –CH– of cyclohexane), 6.11 (s, 1H, NH of pyrrole), 6.67 (s, 1H, CH of pyrrole), 11.02 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 24.6, 27.3, 35.1 (–CH_2– of cyclohexane), δ 53.1 (–CH– of cyclohexane),δ 126.7–101.7 (pyrrole), δ 157.8 (NH–C=O); MS *m/z*: 349.91(M^+), 351.71(M+2); Anal. calcd. for $C_{11}H_{14}Br_2N_2O$ (350.05): C, 37.74; H, 4.03; N, 8.00; Found: C, 37.45; H, 4.23; N, 8.11.

Synthesis of 4,5-dibromo-*N*-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide (3g): 4,5-dibromopyrrol-2-yl trichloromethyl ketone 2 (2.7 mmol), ethanolamine (2.97 mmol) and 0.5 ml of triethyl amine were stirred in 15 ml of Dichloromethane at room temperature for 2 h. After completion of reaction, mixture was diluted with water and extracted with dichloromethane. Organic layer was then evaporated to get crude product. Pure product was obtained by silica gel column chromatography using hexane:ethylacetate (6:4) as white solid in 85 % yield.

4,5-Dibromo-N-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide ***3g*** Brown solid; m.p. 261–263 °C; IR (KBr, cm^{-1}): 3374, 3249, 2931, 1604, 1578; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (q, 2H,–CH_2–NH–), 4.48 (t, 2H, –CH_2–OH), 4.80 (s, 1H, –CH_2–OH), 6.31 (s, 1H, NH of pyrrole), 6.69 (s, 1H, CH of pyrrole), 10.82 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 38.0 (–CH_2–NH–), δ 46.3, δ 69.2 (–CH_2–OH), δ 129.3–101.2 (pyrrole), δ 161.8 (NH–C=O);MS *m/z*: 311.89(M^+), 313.23(M+2); Anal. calcd. for $C_7H_8Br_2N_2O_2$ (311.96): C, 26.95; H, 2.58; N, 8.98; Found: C, 27.03; H, 2.61; N, 8.97.

Synthesis of N-(2-hydroxyethyl)-1H-pyrrole-2-carboxamide (4)

2-Trichloroacetyl pyrrole 1 (2 mmol), ethanolamine (2.1 mmol) and 0.5 ml of triethyl amine were stirred in 15 ml of dichloromethane at room temperature for 2 h. After completion of reaction, mixture was diluted with water and extracted with dichloromethane. Organic layer was then evaporated to get crude product. Pure product was obtained by silica gel column chromatography using hexane:ethylacetate (6:4) as colorless liquid in 85 % yield.

*General procedure for synthesis of simple ester derivatives (**5a–5j**)*

Acid chlorides (2 mmol) were added to 25 ml two necked round bottom flask containing 3 g or 4 (1 equiv) in 15 ml dichloromethane. Triethyl amine 0.5 ml was added dropwise to neutralize the acid liberated during the reaction, finally the reaction mixture was stirred for 1–3 h to get respective product (observed on TLC). This crude product is then subjected to silica gel column chromatography with required percentage of eluent to get pure product in 70–80 % yield.

2-(1H-pyrrole-2-carboxamido)ethyl acetate ***5a*** Brown solid; m.p. 235–237 °C; IR (KBr, cm^{-1}): 3225, 2975, 1745, 1316;^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (s, 3H, C<u>H</u>$_3$–C=O), 3.78 (t, 2H, –CH_2–C<u>H</u>$_2$–NH–), 4.52 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.20 (s, 1H, N<u>H</u> of pyrrole), 6.36 (t, 1H), 6.68 (d, 1H, C<u>H</u> of pyrrole) 7.21 (d, 1H, C<u>H</u> of pyrrole), 10.23 (s, 1H, N<u>H</u>–C=O);^{13}C NMR ($CDCl_3$, 400 MHz): δ 19.6(<u>C</u>H$_3$–C=O), δ 36.9 (–<u>C</u>H$_2$–NH–), δ 68.6(–<u>C</u>H$_2$–O–), δ 129.8–109.2 (pyrrole), δ 160.1 (NH–<u>C</u>=O), δ 175.3 (O=<u>C</u>–O–);MS *m/z*: 196.07(M^+); Anal. calcd. for $C_9H_{12}N_2O_3$ (196.20): C, 55.09; H, 6.16; N, 14.28; Found: C, 55.14; H, 6.31; N, 14.08.

2-(4, 5-Dibromo-1H-pyrrole-2-carboxamido)ethyl acetate ***5b*** Brown solid; m.p. 211–213 °C; IR (KBr, cm^{-1}): 3235, 2960, 1741, 1370;^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29 (s, 3H, C<u>H</u>$_3$–C=O), 3.58 (q, 2H,–CH_2–C<u>H</u>$_2$–NH–), 4.35 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.30 (s, 1H, N<u>H</u> of pyrrole) 6.70 (s, 1H, C<u>H</u> of pyrrole), 10.78 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 24.8 (<u>C</u>H$_3$–C=O), δ 37.6 (–<u>C</u>H$_2$–NH–), δ 69.2 (–<u>C</u>H$_2$–O–), δ 128.0–97.9 (pyrrole), δ 160.1 (NH–<u>C</u>=O), δ 173.4 (O=<u>C</u>–O–); MS *m/z*: 353.91(M^+), 355.90(M+2); Anal. calcd. for $C_9H_{10}Br_2N_2O_3$ (354.00): C, 30.54; H, 2.85; N, 7.91; Found: C, 30.37; H, 2.67; N, 7.87.

2-(1H-pyrrole-2-carboxamido)ethyl benzoate ***5c*** Brown solid; m.p. 253–256 °C; IR (KBr, cm^{-1}): 3336, 3240, 2959, 1710, 1370;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82 (q, 2H,–CH_2–C<u>H</u>$_2$–NH–), 4.45 (t, 2H,–CH_2–C<u>H</u>$_2$–O–), 6.65 (d, 1H, N<u>H</u> of pyrrole), 6.34–6.95 (m, 3H, C<u>H</u> of pyrrole), 7.41–8.32 (m, 5H,Ar<u>H</u>), 10.28 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 41.3 (–<u>C</u>H$_2$–NH–), δ 68.2 (–<u>C</u>H$_2$–O–), δ 129.8–107.3 (pyrrole),δ 132.4 (Ar<u>C</u>H–C=O), δ 137.2–128.6 (Ar–C), δ 160.4 (NH–<u>C</u>=O), δ 174.4 (O=<u>C</u>–O–);MS *m/z*: 258.10(M^+); Anal. calcd. for $C_{14}H_{14}N_2O_3$ (258.27): C, 65.11; H, 5.46; N, 10.85; Found: C, 65.17; H, 5.78; N, 10.43.

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl benzoate ***5d*** Brown solid; m.p. 245–247 °C; IR (KBr, cm^{-1}): 3336, 3240, 2959, 1710, 1370; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (q, 2H, –CH_2–C<u>H</u>$_2$–NH–), 4.55 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.39 (s, 1H, N<u>H</u> of pyrrole), 6.60 (s, 1H, C<u>H</u> of pyrrole), 7.46–7.61 (m, 3H, Ar<u>H</u>), 8.05 (m, 2H, Ar<u>H</u>), 10.28 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.2 (–<u>C</u>H$_2$–NH–), δ 65.5(–<u>C</u>H$_2$–O–), δ 128.2–100.1 (pyrrole),δ 132 (Ar<u>C</u>H–C=O), δ 134.7–128.2 (Ar C), δ 160.3 (NH–<u>C</u>=O), δ 167.4 (O=<u>C</u>–O–); MS *m/z*:415.91(M^+), 417.92(M+2); Anal. calcd. for $C_{14}H_{12}Br_2N_2O_3$ (416.06): C, 40.41; H, 2.91; N, 6.73; Found: C, 40.13; H, 3.01; N, 6.79.

2-(1H-pyrrole-2-carboxamido)ethyl 3,4-dimethoxybenzoate ***5e*** Brown solid; m.p. 240–242 °C; IR (KBr, cm^{-1}): 3430, 2931, 1710, 1018; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83 (s, 6H,(–OC<u>H</u>$_3$)$_2$), 3.85 (q, 2H, –CH_2–C<u>H</u>$_2$–NH–), 4.53 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.31 (s, 1H, N<u>H</u> of pyrrole), 7.15 (m, 1H,Ar<u>H</u>), 7.12–7.32 (m,2H, Ar<u>H</u>), 7.11–7.69 (m, 3H, C<u>H</u> of pyrrole), 10.36 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.8 (–<u>C</u>H$_2$–NH–), δ 56.7 (<u>C</u>H$_3$O–),δ 65.2(–<u>C</u>H$_2$–O–), δ 122.2 (Ar<u>C</u>H–C=O), δ 128.9–110.2 (pyrrole), δ 156.4–110.7 (Ar C), δ 160.2 (NH–<u>C</u>=O), δ 168.9 (O=<u>C</u>–O–); MS *m/z*: 318.12(M^+); Anal. calcd. for $C_{16}H_{18}N_2O_5$ (318.32): C, 60.37; H, 5.70; N, 8.80; Found: C, 60.53; H, 5.78; N, 8.91.

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl 3,4-dimethoxybenzoate ***5f*** Brown solid; m.p. 246–248 °C; IR (KBr, cm^{-1}): 3460, 3388, 1694, 1651, 1230; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 6H, (–OC<u>H</u>$_3$)$_2$),3.98 (q, 2H, –CH_2–C<u>H</u>$_2$–NH–), 4.53 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.47 (s, 1H, N<u>H</u> of pyrrole), 6.84 (s, 1H, C<u>H</u> of pyrrole) 7.46 (s, 1H, Ar<u>H</u>), 7.55–7.81 (m, 2H, Ar<u>H</u>), 10.49 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.3 (–<u>C</u>H$_2$–NH–), δ 56.3 (<u>C</u>H$_3$O–), δ 65.3(–<u>C</u>H$_2$–O–), δ 124.4 (Ar<u>C</u>H–C=O), δ 128.9–99.75 (pyrrole), δ 156.7–110.2 (Ar C), δ 161.7 (NH–<u>C</u>=O), δ 171.9 (O=<u>C</u>–O–); MS *m/z*:475.92(M^+), 477.94 (M+2); Anal. calcd. for $C_{16}H_{16}Br_2N_2O_5$ (476.12): C, 40.36; H, 3.39; N, 5.88; Found: C, 40.36; H, 3.39; Br, 33.56; N, 5.88.

2-(1H-pyrrole-2-carboxamido)ethyl 4-chlorobenzoate ***5g*** Brown solid; m.p. 222–224 °C; IR (KBr, cm^{-1}): 3410, 2935, 1711, 1118; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82 (q, 2H, –CH_2–C<u>H</u>$_2$–NH–), 4.65 (t, 2H, –CH_2–C<u>H</u>$_2$–O–), 6.23 (s, 1H, N<u>H</u> of pyrrole),6.72 (s, 1H, C<u>H</u> of pyrrole), 6.72–6.99 (m,2H, C<u>H</u> of pyrrole), 7.23–7.99 (m, 4H,Ar<u>H</u>), 10.24 (s, 1H, N<u>H</u>–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.7 (–<u>C</u>H$_2$–NH–), δ 65.1(–<u>C</u>H$_2$–O–), δ 127.3–110.1 (pyrrole),134.2 (Ar<u>C</u>H–C=O), δ 135.9 (Ar<u>C</u>H–Cl), δ 140.5–128.8 (ArC), δ 160.2 (NH–<u>C</u>=O), δ 167.3 (O=<u>C</u>–O–); MS *m/z*: 292.08(M^+); Anal. calcd. for $C_{14}H_{13}ClN_2O_3$ (292.72): C, 57.44; H, 4.48; N, 9.57; Found: C, 57.56; H, 4.67; N, 9.23.

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl 4-chlorobenzoate ***5h*** Brown solid; m.p. 254–256 °C; IR (KBr, cm^{-1}): 3396, 3152, 1706, 1440; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.79 (q, 2H, –CH_2–CH_2–NH–), 4.54 (t, 2H, –CH_2–CH_2–O–), 6.37 (s, 1H, NH of pyrrole) 6.81 (s, 1H, CH of pyrrole), 7.35–7.69 (m, 4H,ArH), 10.41 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 38.3 (–CH_2–NH–), δ 68.5 (–CH_2–O–), δ 125.8–101.6 (pyrrole), δ 135.7 (ArCH–Cl), δ 142.4 (ArCH–C=O), δ 142.9–118.2 (Ar C), δ 160.1 (NH–C=O), δ 167.6 (O=C–O–); MS *m/z*: 449.78(M^+), 451.88(M+2); Anal. calcd. for $C_{14}H_{11}Br_2ClN_2O_3$ (450.51): C, 37.32; H, 2.46; N, 6.22; Found: C, 37.46; H, 2.57; N, 6.11.

2-(1H-pyrrole-2-carboxamido)ethyl 2-hydroxybenzoate ***5i*** Brown solid; m.p. 248–250 °C; IR (KBr, cm^{-1}): 3410, 3232, 1708, 1270; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.58 (q, 2H, –CH_2–CH_2–NH–), 4.61 (t, 2H, –CH_2–CH_2–O–), 5.15 (s, 1H, NH of pyrrole), 5.43 (s, 1H, ArOH), 6.99–7.11 (m, 3H, CH of pyrrole), 7.27–7.91 (m, 4H, ArH), 10.56 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.5 (–CH_2–NH–), δ 65.8(–CH_2–O–), δ 112.3 (ArCH–C=O), δ 127.3–109.6 (pyrrole), δ 134.1–116.7 (ArC), δ 159.2 (ArCH–OH), δ 160.2 (NH–C=O), δ164.4 (O=C–O–); MS *m/z*: 274.12(M^+), 276.25(M+2); Anal. calcd. for $C_{14}H_{14}N_2O_4$ (274.27): C, 61.31; H, 5.14; N, 10.21; Found: C, 61.35; H, 5.11; N, 10.42.

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl 2-hydroxybenzoate ***5j*** Brown solid; m.p. 251–253 °C; IR (KBr, cm^{-1}): 3336, 3235, 1705, 1241; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.67 (q, 2H, –CH_2–CH_2–NH–), 4.65 (t, 2H, –CH_2–CH_2–O–), 5.35 (s, 1H, ArOH), 6.15 (s, 1H, NH of pyrrole), 6.93 (d, 1H, CH of pyrrole), 7.31–7.77 (m, 4H, ArH), 10.41 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 39.3 (–CH_2–NH–), δ 64.3(–CH_2–O–), δ 112.9 (ArCH–C=O), δ 128.2–100.1 (pyrrole), δ 134.5–116.8 (Ar C),δ 158.7 (ArCH–OH), δ 160.2 (NH–C=O), δ 164.2 (O=C–O–); MS *m/z*:431.81(M^+), 433.91(M+2); Anal. calcd. for $C_{14}H_{12}Br_2N_2O_4$ (432.06): C, 72.89; H, 4.33; N, 10.63; Found: C, 72.63; H, 4.16; N, 10.37.

*General procedure for synthesis of cinnamic ester derivatives (**6a**–**6n**)*

Acid chlorides (2 mmol) were added to 25 ml two necked round bottom flask containing pyrrole-2-carboxamide 3 g or 4 (2 mmol) in 15 ml dichloromethane. Triethyl amine 0.5 ml was added dropwise to neutralize the acid liberated during the reaction, finally the reaction mixture was stirred for 1–3 h to get respective product observed on TLC. This crude product is then subjected to silica gel column chromatography with required percentage of hexane/ethyl acetate eluent to get pure product in 75–85 % yield.

2-(1H-pyrrole-2-carboxamido)ethylcinnamate ***6a*** Yellow solid; m.p. 234–236 °C; IR (KBr, cm^{-1}): 3286, 2949, 1706, 1320; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.52 (q, 2H, –CH_2–CH_2–NH–), 4.55 (t, 2H, –CH_2–CH_2–O–), 6.44 (s, 1H, NH of pyrrole), 6.55 (d, 1H, Ar–CH=CH–), 6.61 (t, 1H, CH of pyrrole), 6.71 –6. 98 (m, 2H, CH of pyrrole), 7.19 (d, 1H, Ar–CH=CH–), 7.31–7.91 (m, 5H,ArH), 10.28 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.2 (–CH_2NH–), δ 67.0 (–CH_2–O–),δ 126.8–108.0 (pyrrole), δ 135.1–128.5(Ar–C), δ 145.0 (Ar–CH_2=CH_2–), δ 159.7(Ar–CH_2=CH_2–),160.5 δ (NH–C=O), 166.2 δ (O=C–O–); MS *m/z*: 284.14(M^+); Anal. calcd. for $C_{16}H_{16}N_2O_3$ (284.31): C, 67.59; H, 5.67; N, 9.85; Found: C, 67.67; H, 5.69; N, 9.72.

2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl cinnamate ***6b*** Brown solid; m.p. 256–258 °C; IR (KBr, cm^{-1}): 3442, 2935, 1705, 1643, 1219; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.41 (q, 2H, –CH_2–CH_2–NH–), 4.87 (t, 2H, –CH_2–CH_2–O–), 6.32 (s, 1H, NH of pyrrole), 6.43 (d, 1H, CH of pyrrole) 6.81 (d, 1H, Ar–CH=CH–), 7.11 (d, 1H, Ar–CH=CH–) 7.24–7.89 (m, 5H, ArH), 10.67 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.4(–CH_2NH–), δ 67.1 (–CH_2–O–),δ 128.5–100.3(pyrrole),δ 135.1–127.3 (Ar–C), δ 145.4 (Ar–CH_2=CH_2–), δ 156.2(Ar–CH_2=CH_2–),δ 162.5 (NH–C=O), δ 168.6 (O=C–O–); MS *m/z*: 441.94(M^+), 443.93(M+2); Anal. calcd. for $C_{16}H_{14}Br_2N_2O_3$ (442.10): C, 43.47; H, 3.19; N, 6.34; Found: C, 43.58; H, 3.33; N, 6.23.

(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(3,4-dimethoxyphenyl)acrylate ***6c*** Yellow solid; m.p. 245–247 °C; IR (KBr, cm^{-1}): 3419, 2922, 1715, 1635;^1H NMR ($CDCl_3$, 400 MHz): δ 3.46 (q, 2H, –CH_2–CH_2–NH–), 3.89 (s, 6H, –(OCH_3)$_2$), 4.67 (t, 2H, –CH_2–CH_2–O–), 6.15 (s, 1H, NH of pyrrole), 6.37 (d, 1H, Ar–CH=CH–), 6.71 (t, 1H, CH of pyrrole), 6.73 –6. 92 (m, 2H, CH of pyrrole), 7.14 (d, 1H, Ar–CH=CH–) 7.42–7.86 (m, 3H, ArH), 10.87 (s, 1H, NH–C=O);^{13}C NMR ($CDCl_3$, 400 MHz)) δ 39.2 (–CH_2NH–), δ 57.1 (–(OCH_3)$_2$), δ 67.2 (–CH_2–O–), δ 106.8–100.5 (pyrrole), δ 135.5–113.7 (Ar–C),δ 145.3 (Ar–CH_2=CH_2–), δ 166.5 (Ar–CH_2=CH_2–),δ 158.2 (NH–C=O),δ 167.4 (O=C–O–); MS *m/z*:344.10(M^+); Anal. calcd. for $C_{18}H_{20}N_2O_5$ (344.36): C, 62.78; H, 5.85; N, 8.13; Found: C, 62.87; H, 5.61; N, 8.25.

(E)-2-(4,5-dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(3,4-dimethoxyphenyl)acrylate ***6d*** Brown solid; m.p. 252–254 °C; IR (KBr, cm^{-1}): 3246, 2941, 1701, 1638, 1229; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.56 (q, 2H, –CH_2–CH_2–NH–), 4.29 (s, 6H, –(OCH_3)$_2$),4.67 (t, 2H, –CH_2–CH_2–O–), 6.41 (s, 1H, NH of pyrrole), 6.51 (d, 1H, Ar–CH=CH–), 6.73 (d, 1H, CH of pyrrole), 7.24 (d, 1H, Ar–CH=CH–), 7.32–7.87 (m, 3H, ArH), 10.91 (s, 1H,

NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.6 (–$\underline{C}H_2$NH–), δ 56.8 (–(O$\underline{C}H_3$)$_2$), δ 67.6 (–$\underline{C}H_2$–O–), δ 128.5–110.2 (pyrrole), δ 135.1–127.3 (Ar–$\underline{C}$), δ 145.4 (Ar–$\underline{C}H_2$=CH_2–), δ 166.7(Ar–CH_2=$\underline{C}H_2$–),δ 160.1 (NH–$\underline{C}$=O),δ 168.2 (O=$\underline{C}$–O–); MS *m/z*: 501.91(M^+), 503.95(M+2); Anal. calcd. for $C_{18}H_{18}Br_2N_2O_5$ (502.15): C, 43.05; H, 3.61; N, 5.58; Found: C, 43.13; H, 3.12; N, 5.34.

(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(benzo[d][1,3] dioxol-5-yl)acrylate ***6e*** Yellow solid; m.p. 256–258 °C; IR (KBr, cm^{-1}): 3394, 2928, 1708, 1637;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.52 (q, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.71 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 6.11(s, 2H, –O–$\underline{C}H_2$–O–), 6.23 (s, 1H, N$\underline{H}$ of pyrrole), 6.41 (d, 1H, Ar–CH=C$\underline{H}$–), 6.58 (t, 1H, C$\underline{H}$ of pyrrole), 6.63 –6.89 (m, 2H, C$\underline{H}$ of pyrrole), 7.25 (d, 1H, Ar–C$\underline{H}$=CH–) 7.38–7.95 (m, 3H,Ar$\underline{H}$), 10.07 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.1 (–$\underline{C}H_2$NH–), δ 67.3 (–$\underline{C}H_2$–O–),δ 99.2(–O–$\underline{C}H_2$–O–), δ 116.4(Ar–CH_2=$\underline{C}H_2$–), δ 126.8–108.0 (pyrrole), δ 145.3–101.3(dioxo–Ar), δ 145.0 (Ar–$\underline{C}H_2$=CH_2–), δ 160.59 (NH–$\underline{C}$=O),δ 166.2 (O=$\underline{C}$–O–); MS *m/z*: 328.11(M^+); Anal. calcd. for $C_17H_{16}N_2O_5$ (328.32): C, 62.19; H, 4.91; N, 8.53; Found: C, 62.34; H, 4.75; N, 8.42.

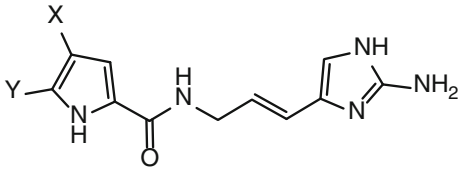
(E)-2-(4,5-dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(benzo [d][1,3]dioxol-5-yl)acrylate ***6f*** Yellow solid; m.p. 258–260 °C; IR (KBr, cm^{-1}): 3280, 2927, 1703, 1625, 1053; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.46 (q, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.56 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 6.01 (s, 2H, –O–$\underline{C}H_2$–O–),6.12 (s, 1H, N$\underline{H}$ of pyrrole), 6.35 (d, 1H, Ar–CH=C$\underline{H}$–), 6.81 (s, 1H, C$\underline{H}$ of pyrrole), 7.21 (d, 1H, Ar–C$\underline{H}$=CH–), 7.29–7.93 (m, 3H, Ar$\underline{H}$), 10.22 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.4(–$\underline{C}H_2$NH–), δ 67.1 (–$\underline{C}H_2$–O–),δ 97.8(–O–$\underline{C}H_2$–O–),δ 114.7(Ar–CH_2= $\underline{C}H_2$–), δ 128.5–100.4 (pyrrole), δ 145.3–101.8(dioxo–Ar), δ 145.4 (Ar–$\underline{C}H_2$=CH_2–), δ 162.5(NH–$\underline{C}$=O), δ 168.9 (O=$\underline{C}$–O–); MS *m/z*: 485.91(M^+), 487.91(M+2); Anal. calcd. for $C_{17}H_{14}Br_2N_2O_5$ (486.11): C, 42.00; H, 2.90; N, 5.76; Found: C, 42.12; H, 2.79; N, 5.79.

(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(naphthalen-2-yl)acrylate ***6g*** Yellow solid; m.p. 267–269 °C; IR (KBr, cm^{-1}): 3410, 3235, 1705, 1642, 1239; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (q, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.61 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 6.19 (s, 1H, N$\underline{H}$ of pyrrole), 6.36 (d, 1H, naphthalene –CH=C$\underline{H}$–), 6.78 (t, 1H, C$\underline{H}$ of pyrrole), 6.89–7.19 (m, 2H, C$\underline{H}$ of pyrrole), 7.35–7.99 (m, 8H, naphthalene –C$\underline{H}$=CH–, naphthalene), 10.09 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 38.9 (–$\underline{C}H_2$NH–), δ 67.5 (–$\underline{C}H_2$–O–),δ 124.2(naphthalene –CH_2=$\underline{C}H_2$–),δ 126.8–107.9 (pyrrole), δ 135.5–125.4 (naphthalene), δ 144.9 (naphthalene –$\underline{C}H_2$=CH_2–), δ 160.5(NH–$\underline{C}$=O), δ 166.5 (O=$\underline{C}$–O–); MS *m/z*: 334.15(M^+); Anal. calcd. for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38; Found: C, 71.67; H, 5.65; N, 8.16.

(E)-2-(4,5-dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(naphthalen-2-yl)acrylate ***6h*** Yellow solid; m.p. 264–266 °C; IR (KBr, cm^{-1}): 3284, 2922, 1718, 1630, 1043; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (q, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.58 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 5.58 (s, 1H, N$\underline{H}$ of pyrrole), 6.62 (d, 1H, naphtalene –CH=C$\underline{H}$–) 6.81 (s, 1H, N$\underline{H}$ of pyrrole), 7.52–7.91(m, 8H, naphthalene –C$\underline{H}$=CH–, naphthalene), 9.60 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.2(–$\underline{C}H_2$NH–), δ 67.3 (–$\underline{C}H_2$–O–),δ 122.8(naphthalene –CH_2=$\underline{C}H_2$–), δ 128.5–100.7 (pyrrole), δ 135.5–124.9 (naphthalene), δ 145.1 (naphthalene–$\underline{C}H_2$=CH_2–), δ 159.8 (NH–$\underline{C}$=O), δ 163.5 (O=$\underline{C}$–O–); MS *m/z*: 491.91(M^+), 494.10(M+2); Anal. calcd. for $C_{20}H_{16}Br_2N_2O_3$ (492.16): C, 48.81; H, 3.28; N, 5.69; Found: C, 48.75; H, 3.16; N, 5.54.

(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(furan-2-yl) acrylate ***6i*** Brown solid; m.p. 230–232 °C; IR (KBr, cm^{-1}): 3337, 3153, 1701, 1637, 1561; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (q, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.56 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 6.48 (s, 1H, N$\underline{H}$ of pyrrole), 6.69 (d, 1H, furan–CH=C$\underline{H}$–),6.71 (t, 1H, C$\underline{H}$ of pyrrole), 6.72 –6.91 (m, 2H, C$\underline{H}$ of pyrrole), 7.19 (d, 1H, furan–C$\underline{H}$=CH–), 7.25–8.09 (m, 3H,furan), 10.36 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.7 (–$\underline{C}H_2$NH–), δ 66.9 (–$\underline{C}H_2$–O–), δ 126.8–108.4 (pyrrole), δ 145.2 (furan–$\underline{C}H_2$=CH_2–), δ 151.5–112.8 (furan), δ 159.4(furan–CH_2=$\underline{C}H_2$–), δ 160.3 (NH–$\underline{C}$=O),δ 166.1(O=$\underline{C}$–O–); MS *m/z*:274.12(M^+); Anal. calcd. for $C_{14}H_{14}N_2O_4$ (274.27): C, 61.31; H, 5.14; N, 10.21; Found: C, 61.45; H, 5.11; N, 10.19.

(E)-2-(4,5-dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(furan-2-yl)acrylate ***6j*** Brown solid; m.p. 235–237 °C; IR (KBr, cm^{-1}): 3393, 1704, 1636, 1563, 1261;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88 (t, 2H, –CH_2–$\underline{C}H_2$–NH–), 4.61 (t, 2H, –CH_2–$\underline{C}H_2$–O–), 6.49 (s, 1H, N$\underline{H}$ of pyrrole), 6.54 (d, 1H, furan–CH=C$\underline{H}$–) 7.15 (d, 1H, furan–C$\underline{H}$=CH–), 7.21 (s, 1H, C$\underline{H}$ of pyrrole),7.65–8.11(m, 3H,furan), 10.23 (s, 1H, N$\underline{H}$–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.2 (–$\underline{C}H_2$NH–), δ 67.4 (–$\underline{C}H_2$–O–), δ 128.5–100.8 (pyrrole), δ 151.5–112.2 (furan),δ 145.5 (furan–$\underline{C}H_2$=CH_2–), δ 154.7–116.8 (furan–CH_2=$\underline{C}H_2$–),δ 161.7 (NH–$\underline{C}$=O),δ 166.3(O=$\underline{C}$–O–);MS *m/z*: 431.91(M^+), 433.92(M+2); Anal. calcd. for $C_{14}H_{12}Br_2N_2O_4$ (432.06): C, 38.92; H, 2.80; N, 6.48; Found: C, 38.85; H, 2.89; N, 6.31.



1a X=Y=H Clathrodin
1b X=Br; Y=H Hymenidin
1c X=Y=Br Oroidin

Fig. 1 Pyrrole-aminoimidazole alkaloids

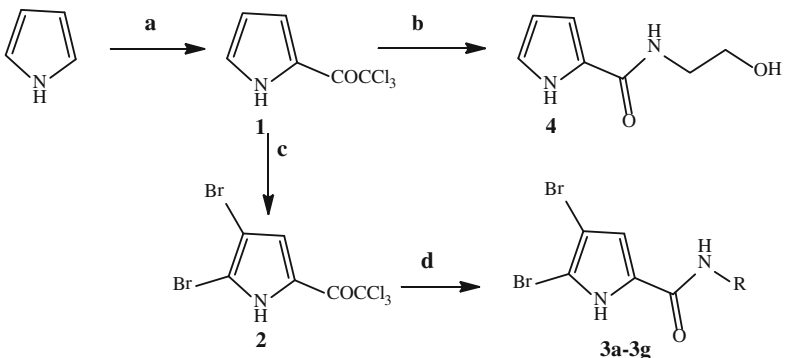
(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(4-nitrophenyl) acrylate ***6k*** Yellow solid; m.p. 256–258 °C; IR (KBr, cm^{-1}): 3396, 3251, 1718, 1643, 1515, 1341; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (t, 2H, –CH_2–CH_2–NH–), 4.62 (t, 2H, –CH_2–CH_2–O–), 6.82 (s, 1H, NH of pyrrole), 6.89 (d, 1H, Ar–CH=CH–) 6.92 (t, 1H, CH of pyrrole), 7.12 –8. 41 (m, 7H, Ar–CH=CH–, CH of pyrrole, ArH), 10.15 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.1 (–CH_2NH–), δ 67.0 (–CH_2–O–),δ 115.2 (Ar–CH_2=CH_2–),δ 126.8–108.2 (pyrrole), δ 147.2–123.6 (*p*-Nitro–Ar–C),δ 145.2 (Ar–CH_2=CH_2–), δ 160.9 (NH–C=O), δ 166.1 (O=C–O–); MS *m/z*: 329.15($M^{+)}$; Anal. calcd. for $C_{16}H_{15}N_3O_5$ (329.31): C, 58.36; H, 4.59; N, 12.76; Found: C, 58.25; H, 4.36; N, 12.91.

(E)-2-(4,5-Dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(4-nitrophenyl)acrylate ***6l*** Brown solid; m.p. 261–263 °C; IR (KBr, cm^{-1}): 3393, 1704, 1636, 1563, 1261;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.53 (t, 2H, –CH_2–CH_2–NH–), 4.18 (t, 2H,–CH_2–CH_2–O–), 5.99 (s, 1H, NH of pyrrole), 6.43 (d, 1H, Ar–CH=CH–), 6.70 (s, 1H, CH of pyrrole), 8.05–8.35 (m, 5H, Ar–CH=CH–,ArH), 10.46 (s, 1H, NH–C=O);^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.1(–CH_2NH–), δ 67.4 (–CH_2–O–),δ 112.4 (Ar–CH_2=CH_2–),δ 128.5–100.2 (pyrrole), δ 147.2–123.8 (*p*-Nitro–Ar–C),δ 145.6(Ar–CH_2=CH_2–),δ 161.9 (NH–C=O), δ 168.9 (O=C–O–); MS *m/z*: 486.92(M^+), 488.91(M+2); Anal. calcd. for $C_{16}H_{13}Br_2N_3O_5$ (487.10): C, 39.45; H, 2.69; N, 8.63; Found: C, 39.29; H, 2.75; N, 8.71.

(E)-2-(1H-pyrrole-2-carboxamido)ethyl 3-(4-(2,4-dichlorophenoxy)phenyl)acrylate ***6m*** Yellow solid; m.p. 275–277 °C; IR (KBr, cm^{-1}): 3396, 3292, 1708, 1623, 1115;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.56 (q, 2H, –CH_2–CH_2–NH–), 4.43(t, 2H, –CH_2–CH_2–O–), 5.68 (s, 1H, NH of pyrrole), 6.79 (d, 1H, Ar–CH=CH–) 6.82 (t, 1H, CH of pyrrole), 7.02 –8. 01 (m, 9H, Ar–CH=CH–, CH of pyrrole, ArH), 10.05 (s, 1H, NH–C=O);^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.2 (–CH_2NH–), δ 67.7 (–CH_2–O–), δ 117.3 (Ar–CH_2=CH_2–),δ 126.8–107.9 (pyrrole),δ 135.5–128.4 (Ar–C), δ 144.8 (Ar–CH_2=CH_2–),δ 150.4–120.6 (Dichloro-Ar–C), δ 160.2 (NH–C=O),δ 166.7 (O=C–O–); MS *m/z*: 444.10(M^+); Anal. calcd. for $C_{22}H_{18}Cl_2N_2O_4$ (445.30): C, 59.34; H, 4.07; N, 6.29; Found: C, 59.59; H, 4.01; N, 6.19.

(E)-2-(4,5-dibromo-1H-pyrrole-2-carboxamido)ethyl 3-(4-(2,4-dichlorophenoxy)phenyl)acrylate ***6n*** Brown solid; m.p. 278–280 °C; IR (KBr, cm^{-1}): 3367, 1711, 1638, 1313, 1211;^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.79 (q, 2H, –CH_2–CH_2–NH–), 4.42 (t, 2H, –CH_2–CH_2–O–), 5.12 (s,

Scheme 1 Synthesis of dibromopyrrole-2-carboxamides (scaffold 1)

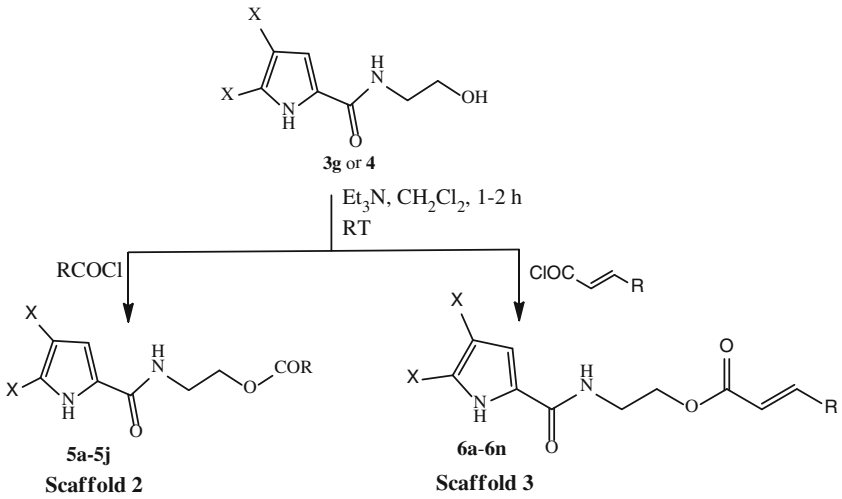


Scaffold1

3a: R= CH_2Ph **3e**: R= CH_3(CH)Ph
3b: R= *n*-Butyl **3f**: R= Cyclohexyl
3c: R= *n*-Hexyl **3g**: R= CH_2CH_2OH
3d: R= *t*-Butyl

Reagents and Conditions: (a) CCl_3COCl, Ether, RT for 2hr and then K_2CO_3; (b) ethanolamine, TEA, CH_2Cl_2,RT for 2 hr; (c) $NaNO_2$/48% HBr 2-4h (d) RNH_2, TEA, CH_2Cl_2, RT for 1-5 hr

Scheme 2 Simple ester and cinnamic ester derivatives of pyrrole-2-carboxamide (scaffold 2 and scaffold 3)



5a: X=H, R=CH_3
5b; X=Br, R=CH_3
5c: X=H, R=Ph
5d: X=Br, R=Ph
5e: X=H, R=3,4-diOMePh
5f: X=Br, R=3,4-diOMePh
5g: X=H, R=4-ClPh
5h: X=Br, R=4-ClPh
5i: X=H, R=2-OHPh
5j: X=Br, R=2-OHPh

6a: X=H, R=Ph
6b; X=Br, R=Ph
6c: X=H, R=3,4-diOMePh
6d: X=Br, R=3,4-diOMePh
6e: X=H, R=3,4-phenylenedioxy
6f: X=Br, R=3,4-$_p$hen$_y$lenediox_y
6g: X=H, R=β-napthyl
6h: X=Br, R=β-napthyl
6i: X=H, R=Furyl
6j: X=Br, R=Furyl
6k: X=H, R=4-nitroPh
6l: X=Br, R=4-nitroPh
6m: X=H, R=4-(2,4-dichlorophenoxy)Ph
6n: X=Br, R=4-(2,4-dichlorophenoxy)Ph

Table 2 Antimicrobial testing results: (MIC μg/ml)

Compounds	X	R	*S. aureus*	*E. coli*
3a	Br	CH_2Ph	62.5	15.62
3b	Br	*n*-Octyl	>125	>125
3c	Br	*n*-Hexyl	>125	>125
3d	Br	*t*-Butyl	>125	62.5
3e	Br	$CH_3(CH)Ph$	1.56	1.56
3f	Br	Cyclohexyl	62.5	>125
3g	Br	CH_2CH_2OH	>125	>125
5a	H	CH_3	>125	>125
5b	Br	CH_3	>125	>125
5c	H	Ph	7.81	31.25
5d	Br	Ph	>125	>125
5e	H	3,4-DiOMePh	>125	>125
5f	Br	3,4-DiOMePh	>125	>125
5g	H	4-ClPh	31.25	62.5
5h	Br	4-ClPh	62.5	>125
5i	H	2-OHPh	15.62	>125
5j	Br	2-OHPh	31.25	>125
6a	H	Ph	>125	62.5
6b	Br	Ph	62.5	>125
6c	H	3,4-DiOMePh	15.62	31.25
6d	Br	3,4-DiOMePh	>125	31.25

Table 2 continued

Compounds	X	R	*S. aureus*	*E. coli*
6e	H	3,4-Phenylenedioxy	>125	>125
6f	Br	3,4-Phenylenedioxy	>125	>125
6g	H	β-Napthyl	>125	62.5
6h	Br	β-Napthyl	31.25	>125
6i	H	Furyl	>125	>125
6j	Br	Furyl	>125	>125
6k	H	4-NitroPh	3.12	>125
6l	Br	4-NitroPh	>125	>125
6m	H	4-(2,4-Dichlorophenoxy)Ph	>125	>125
6n	Br	4-(2,4-Dichlorophenoxy)Ph	>125	>125
Ciprofloxacin[a]	–	–	0.5	0.5

[a] Ciprofloxacin was used as the reference drug

1H, NH of pyrrole), 6.69 (d, 1H, Ar–CH=CH–), 6.87–7.53 (m, 9H, Ar–CH=CH–, CH of pyrrole, ArH), 10.69 (s, 1H, NH–C=O); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 39.1(–CH_2NH–), δ 67.6 (–CH_2–O–), δ 116.8 (Ar–CH_2=CH_2–),δ 128.2–100.3 (pyrrole), δ 135.1–128.2 (Ar–C),δ 145.2 (Ar–CH_2=CH_2–),δ 151.4–123.2 (Dichloro-Ar–C), δ 157.2 (NH–C=O),δ 171.7 (O=C–O–); MS *m/z*: 601.78(M^+), 603.68(M+2); Anal. calcd. for $C_{22}H_{16}Br_2Cl_2N_2O_4$ (603.09): C, 43.81; H, 2.67; N, 4.64; Found: C, 43.73; H, 2.77; N, 4.58.

Current work represents synthesis and antibacterial evaluation of series of Pyrrole-2-carboxamides, scaffold 1 (Fig. 1, Scheme 1), 23 scaffold 2 24 and scaffold 3 25 (Scheme 2). Pyrrole on Trichloroacetylation gave 1 in good yield. Trichloroacetyl pyrrole was then brominated in the presence of our developed reaction conditions which involve Stirring of 1 with 48 % aq HBr in Dichloromethane, $NaNO_2$ was then added portion wise for a minute.

Antimicrobial activity

The series of synthesized molecules were tested against *S. aureus* and *E. Coli* to determine minimum inhibitory concentration (MIC) by Resazurin Microtitre Assay (REMA) plate method with serial dilution. The test compounds were serially diluted on plates with DMSO as a solvent. Homogeneous bacterial culture with 105 cell per well were suspended in microtitre plates. MIC was the lowest inhibition concentration and was observed by colour change of resazurin dye from blue to pink (Tables 1, 2). Ciprofloxacin was used as the reference drug.

Results and discussion

Compound **3a**–**3g** were synthesized with changing R with different alkyl substituents and according to results of scaffold, compound with secondary carbon in alkyl group **3e**, **3f** were found to be more potent than simple alkyl chain carboxamides.

The attempt to increase activity by increasing hydrophilicity through compound **3g** was failed. To remove free hydroxyl group and to check effect of molecular hybridization we combined two active moieties through ester linkage. To check effect of halogen, simple pyrrole derivatives were also synthesized and from biological activity results of scaffold 2. From the compound **4a**–**4j**, simple pyrrole carboxamide **4c** (X = H) was found to be the most active in the series. In the most cases dibromo derivatives showed good activity against *S. aureus* than *E. coli*. Compounds **5a**–**5n** (scaffold 3) was synthesized to find importance of cinnamic acids derivatives in biological activity. All of the compounds showed poor activity against *E. coli* but some compound show promising activity against *S. aureus*. Nitrocinnamate derivative **5k**, showed best biological activity from the series. Further development in this field with special emphasis on cinnamic acid derivatives as antibacterial and antimycobacterial would expect to be more promising.

Conclusions

In conclusion, to the continuation of our previous work on synthesis of pyrrole analogues, especially halopyrrole derivatives, we herein described synthesis and antibacterial evaluation of 31 new compounds with the focus on Oroidin and cinnamic acid framework. Two compounds **3e** and **6k** showed promising activity against both Gram positive and Gram negative bacteria. These may provide potential lead for further development in antimicrobial molecules.

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