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Synthesis and Antimicrobial Activity of Some 1,5-Dioxadiazolyl/Ditriazolyl and Dipyrrolylindole Derivatives

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The exclusive formation of dicarbohydrazide **3** from the indole triester **2** revealed the chemoselectivity of esters at positions 1 and 5 over that of C_3-ester towards nucleophilic attack of hydrazine hydrate. This indole dicarbohydrazide **3** was reacted separately with CS_2/KOH, acetonyl acetone, CS_2, KOH/N_2H_2·H_2O and isothiocyanates to secure 1-(5-mercapto-1,3,4-oxadiazol-2-yl)-methyl-3-ethoxy-carbony l-5-(5-mercapto-1,3,4-oxadiazol-2-yl) methoxy-2-methylindole **5**, 1-(2,5-dimethyl-pyrrol-1-yl)amino-carbonylmethyl-3-ethoxycarbonyl-5-(2,5-dimethylpyrrol-1-yl) amino-carbonylmethoxy-2-methylindole **6**, 1-(4-amino-5-mercapto-1,2,4- triazol-3-yl)methyl-3-ethoxycarbonyl-5-(4-amino-5-mercapto-1,2, 4-triazol-3-yl)methoxy-3-ethoxycarbonyl-2-methyl-indole **7** and 1-(N-substituted thiosemicarbazinocarbonyl) methyl-3-ethoxy-carbonyl/-5-(N substitutedthiosemicarbazinocarbonyl) methoxy-2-methylindoles **8a–b** respectively. The thiosemicarbazides **8a–b** were heated with 4% NaOH to produce 1-(4-substituted-5-mercapto-1,2,4-triazol-3-yl)methyl-5-(4-substituted-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole-3-carboxylic acids **9a–b**. All these new compounds were screened for their antimicrobial activity.

Key Words: Synthesis, Chemoselective, Hydrazine, Indole, Dioxadiazolyl/Ditriazolyl/Dipyrrolyl derivatives.

INTRODUCTION

Heterocyclic compounds occupy a unique place in pharmacology due to their varied biodynamic properties. In particular, indole derivatives are well recognized by their biological properties such as antibacterial, anticancer, antihypertensive, antiinflammatory and antidiabetic[1–4]. The oxadiazoles, pyrroles and triazoles are also known for their interesting pharmacological properties[5–10]. In continuation of our interest in indole derivatives[11, 12], bis/trisheterocycles and chemoselectivity of indole dicarboxylates towards hydrazine hydrate[13], herein, the chemoselectivity of indole tricarboxylates towards hydrazine hydrate and synthesis of hitherto unknown new trisheterocycles wherein oxadiazoles, pyrroles and triazoles are

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linked to position-1 through methylene bridge and position-5 through methyleneoxy bridge of bioactive indole moiety have been reported..

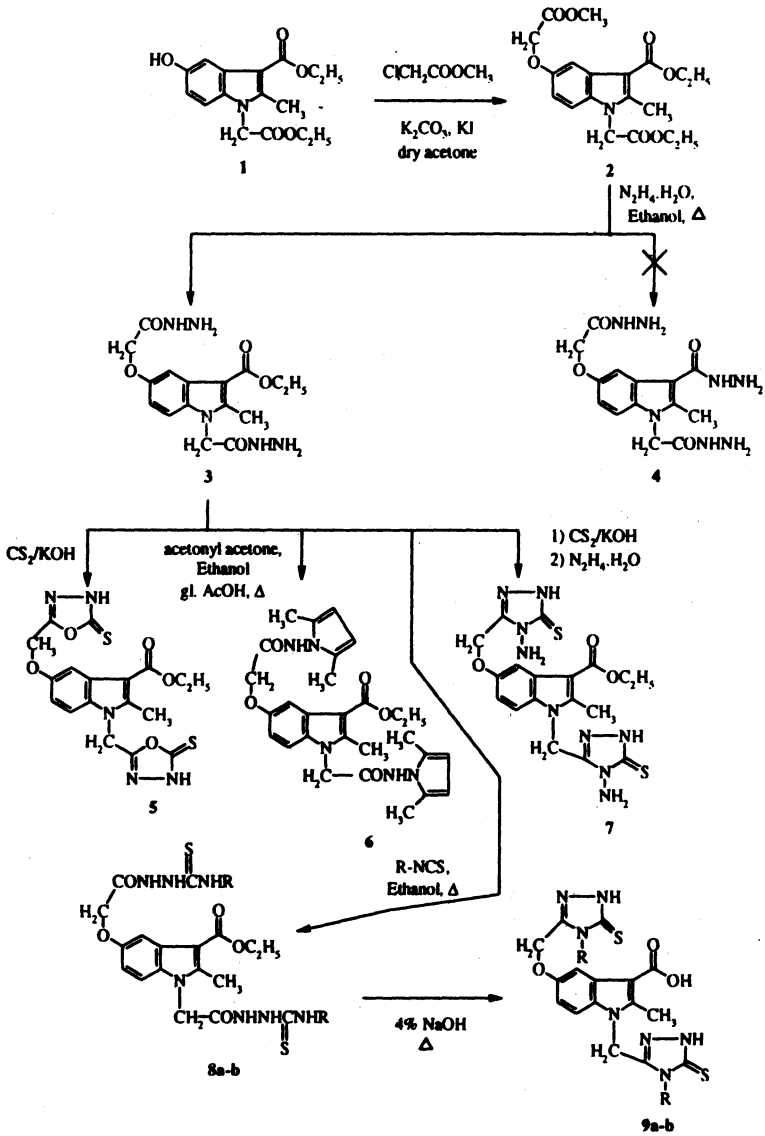
RESULTS AND DISCUSSION

In the present investigation, 1-ethoxycarbonylmethyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole **1** synthesized by Nenitzescu reaction[14] was reacted with methyl chloroacetate and K_2CO_3 in refluxing dry acetone to yield 1-ethoxycarbonylmethyl-3-ethoxycarbonyl-5-methoxycarbonylmethoxy-2-methylindole **2**. When this indole triester **2** was reacted with hydrazine hydrate in boiling ethanol, it produced only the dicarbohydrazide, 1-hydrazinocarbonylmethyl-3-ethoxycarbonyl-5-hydrazinocarbonylmethoxy-2-methylindole **3** without yielding the expected indole tricarbohydrazide **4** which is in conformity with our earlier reports on chemoselectivity[11–13]. Compound **3** on reaction with CS_2, KOH/acetonyl acetone/CS_2, KOH, $N_2H_2{\cdot}H_2O$/isothiocynates produced the desired 1-(5-mercapto-1,3,4-oxadiazol-2-yl)methyl-3-ethoxycarbonyl-5-(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy-2-methylindole **5**, 1-(2,5-dimethylpyrrol-1-yl)aminocarbonyl-methyl-3-ethoxycarbonyl-5-(2,5-dimethylpyrrol-1-yl) aminocarbonylmethoxy-2-methyindole **6**, 1-(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl-3-ethoxycar- bonyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl) methoxy-2-methylindole **7**, 1-(N-substitutedthio-semicarbazinocarbonyl)methyl-3-ethoxycarbonyl-5-(N-substi-tutedthiosemi-carbazinocarbonyl)methoxy-2-methylindole **8a–b**. The thiosemicarbazides **8a–b** on reaction with 4% NaOH yielded 1-(4-substituted-5-mercapto-1,2,4-triazol-3-yl) methyl-3-ethoxycarbonyl-5-(4-substituted-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole-3-carboxylic acids **9a–b** **(Scheme-1).** In the ^1H NMR spectra; the singlets due to C_5-OCH_2- and 1-CH_2-protons of dicarbohydrazides observed at 4.78 and 4.46 respectively were shifted to downfield in trisheterocycles **5, 6, 7** and **9a–b** and found in the range of 5.15–5.68 (C_5-O-CH_2-) and 4.78–5.49 (—N—CH_2) respectively indicating the formation of heterocycles. The structures of all the new compounds were confirmed on the basis of their spectral and analytical data.

Antimicrobial activity

All the new compounds synthesized were screened for their antibacterial activity against Gram-positive bacterium *Micrococcus* and Gram-negative bacterium *E. coli* using norfloxacin as a standard and for antifungal activity against *Penicillium* and *Aspergillus niger* using griseofulvin as standard. Cup-plate method[15, 16] was employed using nutrient agar as culture medium. Test solution was prepared by dissolving 1 mg (1000 g) of compound in 1 mL of DMF and 0.1 mL (100 g) of this solution was used for testing. The zones of inhibition were measured in mm (12–16, 17–21 and 22–30 mm for weak, moderate and highly active zones respectively). Norfloxacin showed a zone of inhibition of 25 mm for *Micrococcus* and 28 mm for *E. coli*. Griseofulvin exhibited a zone of inhibition of 30 mm for both *Penicillium* and *Aspergillus niger*. The screening results revealed that the compounds **7, 8b** and **9b** exhibited moderate activity towards both *Micrococcus* and *E. coli* while the compound **2** displayed moderate activity

towards *Micrococcus* and weak activity towards *E. coli*. Compound **8a** was inactive towards both bacteria and compound **4** was inactive towards *Micrococcus* and weakly active towards *E. coli*. Rest of the compounds showed weak activity. Compounds **2** and **9b** were moderately active towards both fungi. Compound **5** was weakly active towards *A. niger* and moderately active towards *Penicillum*. Rest of the compounds displayed weak activity towards both fungi (Table-1).



Scheme-1

TABLE-1
ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS

Compd.	Zone of inhibition after 48 h			
	Micrococcus	*E. coli*	*Penicillium*	*A. niger*
2	++	+	++	++
4	–	+	+	+
5	+	+	++	+
6	+	+	+	+
7	++	++	+	+
8a	–	–	+	+
8b	++	++	+	+
9a	+	+	+	+
9b	++	++	++	++

(–) = inactive, (+) = weakly active (12–16 mm), (++) = moderately active (17–21 mm), (+++) = highly active (22–30 mm).

EXPERIMENTAL

Melting points were recorded in open capillary tubes and are uncorrected. IR spectra were recorded on Nicolet-Impact 410 spectrometer and Thermo Nicolet spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Av Brucker 300 MHz and AMX 400 MHz spectrophotometers. Mass spectra were recorded on EI-70 Evs spectometer. FAB mass spectra was recorded on a JEOL SX 102/DA-6000 spectrometer. Elemental analysis was carried out on Heraeus CHN rapid analyzer.

1-Ethoxycarbonylmethyl-3-ethoxycarbonyl-5-methoxycarbonylmethoxy-2-methylindole (2)

To the solution of 5-hydroxyindole **1** (6.1 g, 0.02 mol) in dry acetone (100 mL) were added methyl chloroacetate (2.16 g, 0.02 mol), anhydrous K_2CO_3 (6 g) and KI (0.1 g). The reaction mixture was heated at reflux for 50 h. The solution was filtered hot and the solvent was removed under reduced pressure. The residue was collected and recrystallized from suitable solvent.

IR (KBr, cm^{-1}): 1752 and 1734 ν(C_5 and 1-ester C=O), 1672 ν(C_3-ester C=O) and absent ν(C_5—OH); ^{1}H NMR ($CDCl_3$/TMS): δ 1.27 (t, J = 7.1 Hz, 3H, 1-ester CH_3), 1.46 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.73 (s, 3H, C_2—CH_3), 3.83 (s, 3H, C_5-ester CH_3), 4.24 (q, J = 7.1 Hz, 2H, 1-ester CH_2), 4.39 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.73 (s, 2H, NCH_2), 4.81 (s, 2H, OCH_2), 6.96 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.14 (d, J = 8.5 Hz, 1H, C_7—H) and 7.64 (d, J = 2.5 Hz, 1H, C_4—H).

1-Hydrazinocarbonylmethyl-3-ethoxycarbonyl-5 hydrazinocarbonyl-methoxy-2-methylindole (3)

A mixture of indole tricarboxylate **2** (7.54 g, 0.02 mol) in ethanol (100 mL),

hydrazine hydrate (99%) (2 g, 0.04 mol) and pyridine (2 drops) was heated on a boiling water bath for 20 h and concentrated to half volume and left overnight. The separated solid was filtered, washed with little ethanol and recrystallized from suitable solvent. IR (KBr, cm^{-1}): 3318, 3313 and 3224 ν(NH/NH_2), 1689, 1652 ν(C_1, C_5 amide C=O and C_3-ester C=O); ^1H NMR (DMSO-d_6/TMS): δ 1.35 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.65 (s, 3H, C_2—CH_3), 4.25 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.46 (s, 2H, NCH_2), 4.78 (s, 2H, C_5—OCH_2), 6.87 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.33 (d, J = 8.5 Hz, 1H, C_7—H), 7.47 (d, J = 2.5 Hz, 1H, C_4—H), 9.33 (s, 1H, amide NH, vanished on D_2O exchange) and 9.47 (s, 1H, amide NH, disappeared on D_2O exchange).

1-(5-Mercapto-1,3,4-oxadiazol-2-yl)methyl-3-ethoxycarbonyl-5-(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy-2-methylindole (5)

A mixture of indole dicarbohydrazide **3** (0.4 g, 0.001 mol) in ethanol (20 mL), KOH (0.22 g, 0.004 mole) dissolved in water (3 mL) and CS_2 (0.46 g, 0.006 mole) was heated under reflux until the evolution of H_2S ceased (about 25 h). The reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). It was then neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and the dried product was recrystallized from suitable solvent. IR (KBr, cm^{-1}): 3125 and 3085 ν(oxadiazole NH), 1659 ν(C_3-ester C=O) and 1185 ν(C=S); ^1H NMR (DMSO-d_6/TMS): δ 1.36 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.72 (s, 3H, C_2-CH_3), 4.27 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 5.24 (s, 2H, NCH_3), 5.67 (s, 2H, OCH_2), 6.97 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.54 (d, J = 8.5 Hz, 1H, C_7—H), 7.58 (d, J = 2.5 Hz, 1H, C_4—H) 8.32 (s, 1H, oxadiazole NH, disappeared on D_2O exchange) and 8.46 (s, 1H, oxadiazole NH, vanished on D_2O exchange).

1-(2,5-Dimethylpyrrol-1-yl)aminocarbonylmethyl-3-ethoxycarbonyl-5-(2,5-dimethylpyrrol-1-yl)aminocarbonylmethoxy-2-methylindole 6

To a suspension of dicarbohydrazide **3** (0.4 g, 0.001 mol) in ethanol (25 mL) was added acetonyl acetone (0.22 g, 0.02 mol) and glacial acetic acid (1 mL) and the reaction mixture was heated on a boiling water bath for 4 h. The reaction mixture was concentrated to half of its original volume and poured into crushed ice (50 g). The separated solid was filtered, washed with water, dried and recystallized from suitable solvent. IR (KBr, cm^{-1}): 3259 ν(1-amide NH and C_5-amide NH) and 1690 ν(C_3-ester, 1-amide and C_5-amide carbonyls); ^1H NMR (DMSO-d_6/TMS): δ 1.34 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 1.93 (s, 6H, pyrrole CH_3), 1.97 (s, 6H, pyrrole CH_3), 2.70 (s, 3H, C_2—CH_3), 4.29 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.78 (s, 2H, N—CH_2—), 5.15 (s, 2H, —OCH_2), 5.62 (s, 4H, C_3' and C_4'-H of two pyrroles), 6.98 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.51 (d, J = 8.5 Hz, 1H, C_7—H), 7.60 (d, J = 2.5 Hz, 1H, C_4—H), 10.99 (s, 1H, amide NH, vanished on D_2O exchange) and 11.10 (s, 1H, amide NH disappeared on D_2O exchange). ^{13}C NMR (DMSO-d_6) : δ 11.0 (pyrrole CH_3 C), 11.8 (C_3-ester CH_3C), 14.5 (C_2—CH_3C), 44.3 (NCH_2C), 59.1 (C_3-ester CH_2C), 67.0 (C_5—OCH_2C), 103.1 (C_7), 103.3 (C_6), 104.9 C_3' and C_4' of pyrrole), 110.5 (C_4), 111.7 (C_3), 126.8 (junction [b]C), 127.0 C_2'— and C_5'— of pyrrole), 131.9 (junction

[a]C), 146.0 (C_2), 153.6 (C_5), 165.0 (1-amide carbonyl carbon), 166.7 (C_5-amide carbonyl carbon), 168.0 (C_3-ester carbonyl carbon). FABMS (m/z, relative intensity): 519 (M^+, 26), 474 (5), 460 (18), 445 (2), 426 (4), 391 (35), 382 (6), 341 (2), 307 (28), 289 (20), 154 (100), 136 (75).

1-(4-Amino-5-mercapto-1,2,4-triazol-3-yl)methyl-3-ethoxycarbonyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole (7)

To an ice-cold solution of KOH (0.34 g, 0.006 mol) in dry ethanol (50 mL) was added indole dicarbohydrazide 3 (0.8 g, 0.002 mol) and CS_2 with stirring. The reaction mixture was then stirred further at room temperature for 20 h. This mixture was then diluted with dry ether (50 mL) and the precipitated solid was filtered, washed with dry ether and dried to secure the potassium salt of dithiocarbazinic acid. This salt was heated with stirring on a boiling water bath with hydrazine hydrate (2 mL, 0.04 mole) and water (1 mL) till the evolution of H_2S ceased (about 2 h). The reaction mixture was poured into ice-cold water (25 mL) and acidified with acetic acid. The precipitated triazolylindole was filtered, dried and recrystallised from suitable solvent (Table-1). IR (KBr, cm^{-1}): 3300, 3180 ν(NH/NH_2), 1672 ν(C_3-ester CO) and 1170 ν(C═S); ^1H NMR (DMSO-d_6/TMS): δ 1.33 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.74 (s, 3H, C_2—CH_3), 4.29 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 5.10 (s, 4H, NH_2, vanished on D_2O exchange), 5.49 (s, 2H, NCH_2), 5.64 (s, 2H, OCH_2), 6.92 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.42 (d, J = 8.5Hz, 1H, C_7—H), 7.60 (d, J = 2.5 Hz, 1H, C_4—H) and 13.48 (br, 2H, triazole NH, disappeared on D_2O exchange). MS (m/z, relative intensity): 475 (M^+, 10), 427 (10), 419 (30), 383 (44), 246 (50), 232 (18), 218 (22), 174 (25), 160 (20) and 137 (100).

1-(N-substitutedthiosemicarbazinocarbonyl)methyl-3-ethoxycarbonyl-5-(N-substitutedthiosemicarbazinocarbonyl)methoxy-2-methylindoles (8a–b)

General Procedure: To a solution of dicarbohydrazide 3 (0.001 mol) in ethanol (50 mL) was added isothiocyanate (0.002 mol) with stirring. The mixture was heated under reflux for 4 h and part of the solvent was evaporated. The solid that separated on cooling to room temperature was filtered, washed with ethanol and recrystallised from suitable solvents.

Compound 8a: IR (KBr, cm^{-1}): 3450 and 3265 ν(NH), 1690 ν(C_3-ester CO) and 1183 ν(C═S); ^1H NMR (DMSO-d_6/TMS): δ 1.02–1.10 (m, 6H, ethyl CH_3), 1.37 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.66 (s, 3H, C_2—CH_3), 4.31 (q, J = 7.1 Hz, C_3-ester CH_2), 4.59 (s, 2H, NCH_2), 4.93 (s, 2H, OCH_2), 6.95 (d, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.37 (d, J = 8.5 Hz, 1H, C_7—H), 7.62 (d, J = 2.5 Hz, 1H, C_4H), 7.90 (s, 1H, NH, vanished on D_2O exchange), 8.05 (s, 1H, NH, vanished on D_2O exchange), 9.22 (s, 2H, NH, vanished on D_2O exchange), 9.62 (s, 1H, NH, disappeared on D_2O exchange) and 10.22 (s, 1H, NH, vanished on D_2O exchange).

Compound 8b: IR (KBr, cm^{-1}): 3317, 3228 ν(NH), 1694 and 1672 ν(C_3-ester, 1-thiomide and C_5-thioamide carbonyls). ^1H NMR (DMSO-d_6): 1.37 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.69 (s, 3H, C_2—CH_3), 4.29 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.66 (s, 2H, NCH_2), 5.17 (s, 2H, C_5—OCH_2), 6.90–7.58 (m, 11H, C_6, C_7, C_4 and Ar—H), 9.60 (br, 1H, NH, vanished on D_2O exchange), 9.82 (br,

3H, NH, disappeared on D_2O exchange), 10.33 (s, 1H, NH, vanished on D_2O exchange) and 10.51 (br, 1H, NH, disappeared on D_2O exchange).

1-(4-Substituted-5-mercapto-1,2,4-triazol-3-yl)methyl-5-(4-substituted-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole-3-carboxylic acids (9a-b)

General procedure: The suspension of thiosemicarbazides **8a–b** (0.001 mol) in NaOH solution (4%, 10 mL) was refluxed for about 5 h and the reaction mixture after cooling to room temperature was poured into crushed ice (20 g) and acidified carefully with dilute acetic acid. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from suitable solvents (Table-1).

Compound 9a: IR (KBr, cm^{-1}): 3426 and 3169 ν(NH and C_3—COOH), 1661 ν(C_3—C=O) and 1184 (C=S); ^1H NMR (DMSO-d_6/TMS): 1.15 (t, J = 7.1 Hz, 3H, ethyl CH_3), 1.30 (t, J = 7.1 Hz, 3H, ethyl CH_3), 2.67 (s, 3H, C_2—CH_3), 4.07 (q, J = 7.1 Hz, 4H, ethyl CH_2), 5.28 (s, 2H, NCH_2), 5.68 (s, 2H, OCH_2), 6.94 (dd, J = 8.5 Hz and 2.5 Hz, 1H, C_6—H), 7.49 (d, J = 8.5 Hz, 1H, C_7—H), 7.66 (d, J = 2.5 Hz, 1H, C_4—H), 12.14 (br, 1H, C_3-carboxylic OH, vanished on D_2O exchange), 13.60 (br, 1H, triazole NH, disappeared on D_2O exchange) and 13.79 (br, 1H, triazole NH, vanished on D_2O exchange).

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