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Synthesis and Antimicrobial Activity of Novel 1-(4,5-Bioxadiazolyltriazolyl)/1-(4,5-bipyrrolyl-aminocarbonyl)/triazolyl)ethylindole/benz(g)indole

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The exclusive formation of 1-[bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **2** and 1-[bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole **8** from the reaction of 1-[4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **1** and 1-[4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz (g)indole **7** with hydrazine hydrate respectively revealed the chemoselectivity of the C_4 and C_5-esters of triazolylindole over that of C_3-ester towards the nucleophilic attack of hydrazine hydrate. These dicarbohydrazides **2** and **8** were reacted separately with acetonyl acetone and CS_2/KOH to secure 1-[4,5-bis(2,5-dimethyl-pyrrol-1-yl) aminocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **5** and 1-[4,5-bis(2,5-dimethyl-pyrol-1-yl)aminocarbonyl-1,2,3-triazol-1-yl] ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole **9** and 1[4,5-bis(5-mercapto-1,3,4-oxadiazol-2-yl)-1,2,3-triazol-1-yl] ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **6** and 1-[4,5-bis(5-mercapto-1,3,4-oxadiazol-2-yl)-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-methoxy-2-methylbenz(g)indole **10** respectively. All these newly synthesized compounds were screened for their antimicrobial activities.

Key Words: Synthesis, Antimicrobial activity, Indole.

INTRODUCTION

Wide spectrum of biological properties[1–4] have been exhibited by indoles. 1,2,3-Triazoles are endowed with wide range of applications in synthetic, analytical, medicinal, agrochemical and photographic chemisty[5–8]. Pyrroles and oxadiazoles have also displayed interesting pharmacological properties[9–13]. In view of all the above versatile and interesting properties shown by the above heterocycles and also in continuation of our earlier work on indole derivatives[14, 15], it was thought of considerable interest to undertake the synthesis of novel bis-heterocycles wherein biologically active indole moiety is linked at position-1 *via* ethylene bridge to triheterocyclic moiety.

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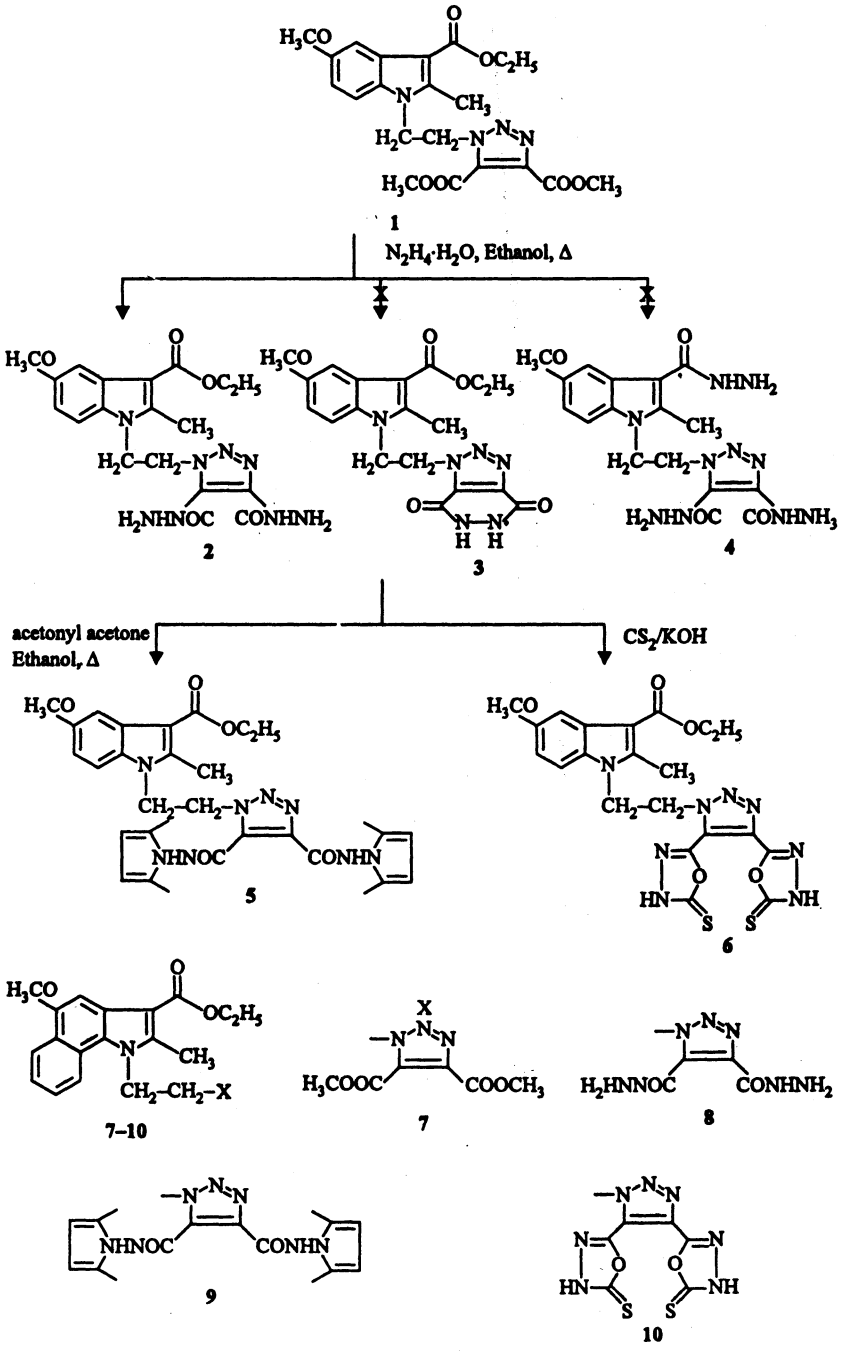
RESULTS AND DISCUSSION

The required starting material, 1-[4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl] ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **1** prepared earlier[16] was reacted with hydrazine hydrate in refluxing ethanol with an expectation of obtaining dicarbohydrazide **2**, pyridazine derivative **3** and tricarbohydrazide **4**. However, the only product obtained was the dicarbohydrazide, 1-[bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl] ethyl-3-etho- xycarbonyl-5-methoxy-2-methylindole **2** indicating the chemoselectivity of triazolyl diesters over that of C_3-ester group towards the nucleophilic attack of hydrazine hydrate which is in conformity of previous reports[14, 15]. Similarly, 1-[4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl] ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole[16] **7** was also reacted with hydrazine hydrate to produce only 1-[bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz[g]indole **8**. These dicarbohydrazides **2** and **8** were further reacted separately with acetonyl acetone and CS_2/KOH to secure 1-[4,5-bis(2,5-dimethylpyrrol-1-yl)aminocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole **5** and 1-[4,5-bis-(2,5-dimethylpyrrol-1-yl)aminocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole **9** and 1-[4,5-bis(5-mercapto-1,3,4,-oxadiazol-2-yl)-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methyl indole **6** and 1-[4,5-bis(5-mercapto-1,3,4-oxadiazol-2-yl)-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole **10** respectively **(Scheme-1)**. The structures of all these newly synthesized compounds were confirmed on the basis of their spectral and analytical data.

Antimicrobial activity

All the new compounds were screened for their antibacterial activity against Gram-positive bacterium *Micrococcus* and Gram-negative bacterium *Escherichia coli* using norfloxacin as a standard and for antifungal activity against *Penicillium* and *Aspergillus niger* using griseofulvin as standard. Cup-plate method[17, 18] was employed using nutrient agar as culture medium. Test solution was prepared by dissolving 1 mg (1000 μg) of compound in 1 mL of DMF and 0.1 mL (100 μg) of this solution was used for testing. The zones of inhibition were measured in mm (12–16 mm, 17–21 mm, 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 inhibtion of 30 mm for both *Penicillium* and *Aspergillus niger.* The screening results revealed that the compounds **2** and **5** were moderately active towards both *Micrococcus* and *E. coli* and compounds **8** and **9** were moderately active towards *E. coli* and weakly active towards *Micrococcus.* Compound **10** was weakly active towards *E. coli* and moderately active towards *Micrococcus.* Compounds **5** and **8** were moderately active towards both *Penicillium* and *A. niger* and rest of the compounds were weakly active towards both fungi (Table-1).


1
$N_2H_4 \cdot H_2O$, Ethanol, Δ
2
3
4
acetonyl acetone
Ethanol, Δ
CS_2/KOH
5
6
7–10
7
8
9
10

Scheme-1

TABLE-1
ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS

Compound	Zone of inibition after 48 h			
	Micrococcus	*E. coli*	*Penicillium*	*A. niger*
2	++	++	+	+
5	++	++	++	++
6	+	+	+	+
8	+	++	++	++
9	+	++	+	+
10	++	+	+	+

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

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 881 and Thermo Nicolet spectrometers. ^1H NMR and ^{13}C NMR spectra in $CDCl_3$ or DMSO-d_6 were recorded on AMX 400 MHz and Brucker's 300 MHz NMR spectrometers (chemical shift in δ ppm). FAB mass spectra were recorded on a JEOL SX 102/DA-6000 spectrometer/Data system using argon/xenon (6 kV, 10 mA) as the FAB gas. Elemental analysis was carried out on Heraeus CHN rapid analyzer.

1-[Bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole (2)

A mixture of triazolylindole triester **1** (0.650 g, 0.0015 mol) in ethanol (50 mL), hydrazine hydrate (99%) (0.15 g, 0.003 mol) and pyridine (2 drops) were heated on a boiling water bath for 3 h and concentrated to half volume and left overnight. The separated solid was filtered, washed with little ethanol and recrystallized from ethanol, yield 0.4 g, 62%, m.p. 246°C (white flowery crystals). IR (KBr, cm^{-1}): 3345, 3314, 3302, 3252 ν(NH/NH_2), 1678 and 1641 ν(C_3-ester and triazolyl amide carbonyls). ^1H NMR (DMSO-d_6/TMS): δ 1.35 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.50 (s, 3H, C_2—CH_3), 3.76 (s, 3H, C_5—OCH_3), 4.24 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.71 (t, J = 7.1 Hz, 2H, indole NCH_2), 5.10 (t, J = 7.1 Hz, 2H, triazole NCH_2), 6.76 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.28 (d, J = 8.5 Hz, 1H, C_7—H), 7.45 (d, J = 2.5 Hz, 1H, C_4—H), 12.03 (s, 2H, amide NH, vanished on D_2O exchange). FABMS, (m/z, relative intensity): 444 (M^+, 30), 445 (M + 1, 20), 412 (6), 399 (72), 367 (10), 246 (20), 206 (6), 188 (12) and 138 (100). Anal., Found: C, 51.48; H, 5.66; N, 25.13. $C_{19}H_{24}N_8O_5$ requires: C, 51.35; H, 5.44; N, 25.21.

1-[4,5-bis(2,5-dimethylpyrrol-1-yl)aminocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole (5).

To the suspension of triazolylindole dicarbohydrazide **2** (0.45 g, 0.001 mol) in ethanol (50 mL) was added acetonyl acetone (0.46 g, 0.004 mol) and glacial acetic

acid (1 mL) and 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 recrystallized from ethanol, yield 0.5 g, 84%, m.p. 169°C (brown granules). IR (KBr, cm^{-1}): 3431 ν(NH), 1696 and 1684 ν(C_3-ester and amide carbonyls); ^1H NMR (DMSO-d_6/TMS): 1.34 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.00 (s, 12H, pyrrole CH_3), 2.53 (s, 3H, C_2—CH_3), 3.73 (s, 3H, C_5—OCH_3), 4.27 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.75 (t, J = 7.1Hz, 2H, indole NCH_2), 5.04 (t, J = 7.1 Hz, 2H, triazole NCH_2), 5.67 (s, 2H, pyrrole C_3— and C_4'—H), 5.69 (s, 2H, pyrrole C_3— and C_4—H), 6.70 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.08 (d, J = 8.5 Hz, 1H, C_7—H), 7.43 (d, J = 2.5 Hz, 1H, C_4—H), 11.91 (s, 1H, NH, vanished on D_2O exchange) and 12.20 (s, 1H, NH, disappeared on D_2O exchange). Anal., Found: C, 61.72; H, 6.31; N, 18.86. $C_{31}H_{36}N_8O_5$ requires: C, 61.99, H, 6.04; N, 18.65.

1-[4,5-Bis(5-mercapto-1,3,4-oxadiazol-2-yl)-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylindole (6)

A mixture of triazolylindole dicarbohydrazide **2** (0.65 g, 0.0015 mol) in ethanol (20 mL), KOH (0.32 g, 0.006 mol) dissolved in water (3 mL) and CS_2 (0.68 g, 0.009 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 crushed ice (50 g). It was then neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and dried product was recrystallized from ethanol, yield 0.5 g, 65%, m.p. 203–4°C (white granules). IR (KBr, cm^{-1}): 3546, 3404 ν(oxadiazole NH), 1683 ν(C_3-ester CO) and 1164 (C=S); ^1H NMR (DMSO-d_6/TMS): 1.36 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.56 (s, 3H, C_2—CH_3), 3.78 (s, 3H, C_5—OCH_3), 4.29 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.78 (t, J = 7.1 Hz, 2H, indole NCH_2), 4.81 (t, J = 7.1 Hz, 2H, triazole NCH_2), 6.78 (dd, J = 8.5 and 2.5 Hz, 1H, C_6—H), 7.30 (d, J = 8.5 Hz, 1H, C_7—H), 7.48 (d, J = 2.5 Hz, 1H, C_4—H), 8.48 (s, 1H, NH, vanished on D_2O exchange) and 13.08 (s, 1H, NH, disappeared on D_2O exchange).

1-[Bis-4,5-hydrazinocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole (8)

This compound **8** was prepared from **7** (0.5 g, 0.001 mol) according to the procedure given for compound **2** and recystallized from ethanol, yield 0.35 g, 70%, m.p. 234–5°C (colourless flakes). IR (KBr, cm^{-1}) : 3448, 3267, 3213, 3142 ν(NH/NH_2), 1662 and 1642 ν(C_3-ester and triazole amide carbonyls); ^1H NMR ($CDCl_3$ DMSO-d_6/TMS): 1.46 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.71 (s, 3H, C_2—CH_3), 4.06 (s, 3H, C_5—OCH_3), 4.42 (q, J = 7.1 Hz, 2H, C_3-ester CH_2), 4.91 (br, 4H, NH_2, vanished on D_2O exchange), 5.12 (t, J = 7.1 Hz, 2H, indole NCH_2), 5.35 (t, J = 7.1 Hz, 2H, triazole NCH_2), 7.45–7.67 (m, 2H, C_7 and C_8—H), 7.75 (s, 1H, C_4—H), 8.41 (d, J = 8.5 Hz, 1H, C_6—H) and 8.44 (d, J = 8.5 Hz, 1H, C_9—H). FABMS (m/z, relative intensity): 494 (M^+, 40), 480 (10), 460 (10), 449 (25), 435 (6), 391 (18), 345 (20) and 154 (100). Anal., Found: C, 55.69; H, 5.34; N, 22.52. $C_{23}H_{26}N_8O_5$ requires: C, 55.86, H, 5.29; N, 22.66.

1-[4,5-Bis(2,5-dimethylpyrrol-1-yl)aminocarbonyl-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole (9)

This compound **9** was prepared from **8** (0.5 g, 0.001 mol) according to the procedure given for compound **5** and recrystallized from ethanol-dioxane, yield 0.48 g, 73%, m.p. 192–3°C (pale pinkish granules). IR (KBr, cm^{-1}): 3268 ν(NH) and 1697 ν(C_3-ester and amide carbonyls); ^1H NMR (DMSO-d_6/TMS): 1.47 (t, J = 7.1 Hz, 3H, C_3-ester CH_3), 2.07 (s, 6H, pyrrole CH_3), 2.13 (s, 6H, pyrrole CH_3), 2.68 (s, 3H, C_2—CH_3), 3.94 (s, 3H, C_5—OCH_3), 4.38 (q, J = 7.1 Hz, 2H, C_3-ester, CH_2), 5.18 (t, J = 7.1 Hz, 2H, indole NCH_2), 5.42 (t, J = 7.1 Hz, 2H, triazole NCH_2), 5.75 (s, 2H, C_3— and C_4—H of pyrrole), 5.79 (s, 2H, pyrrole C_3'— and C_3'—H), 7.44–7.63 (m, 2H, C_7 and C_8—H), 7.76 (s, 1H, C_4—H), 8.39–8.48 (m, 2H, C_6 and C_9—H), 12.18 (s, 1H, NH, vanished on D_2O exchange), 13.02 (s, 1H, NH, disappeared on D_2O exchange). ^{13}C NMR (DMSO-d_6): 10.9 (pyrrole methyl C), 11.1 (C_3-ester methyl C), 14.2 (C_2-methyl C), 44.8 (triazole NCH_2 C), 49.6 (indole NCH_2 C), 55.3 (C_5-methoxy C), 59.1 (C_3-ester methylene C), 98.2 (C_3), 103.2 (C_9), 103.6 (pyrrole C_3—), 105.0 (pyrrole C_4—), 120.0 (C_6), 121.9 (C_4), 122.9 (C_7), 123.1 (C_8), 123.2 and 123.4 (junction C of naphthalene), 124.1 (junction [b] C), 126.8 (C_2), 126.9 (C_2— and C_5— of pyyrole), 131.6 (C_4 of triazole), 137.9 (C_5 of triazole), 143.0 (junction [a] C), 150.5 (C_5), 156.8 (amide carbonyl C), 159.5 (amide carbonyl C), 164.9 (C_3-ester carbonyl C), FABMS (m/z, relative intensity): 650 (M^+, 90), 605 (72), 557 (40), 391 (20), 209 (4), 154 (100) and 136 (70). Anal., found: C, 64.72; H, 5.96; N, 17.13. $C_{35}H_{38}N_8O_5$ requires: C, 64.60; H, 5.89; N, 17.22.

1-[4,5-Bis(5-mercapto-1,3,4-oxadiazol-2-yl)-1,2,3-triazol-1-yl]ethyl-3-ethoxycarbonyl-5-methoxy-2-methylbenz(g)indole (10)

This compound **10** was prepared from **8** (0.5 g, 0.001 mol) according to the procedure depicted for compound **6** and recrystallized from ethanol-dioxane, yield 0.45 g, 665, m.p. 213–4° (dark brown flakes). IR (KBr, cm^{-1}): 3175 ν(oxadiazole NH) and 1672 ν(C_3-ester CO). FABMS (m/z, relative intensity): 578 (M^+, 70), 533 (45), 477 (4), 209 (4) and 102 (22).

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