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REVIEW

Synthesis, characterization and antimicrobial evaluation of novel urea, sulfonamide and acetamide 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one derivatives

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KEYWORDS

Dihydropyrazino[1,2-a]indol-1(2H)-one;
Dihydropyrazino[1,2-a]indol derivatives of urea;
Sulfonamide;
Acetamide;
Antibacterial;
Antifungal

Abstract Series novel of 2-(substituted)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **(4a–e)** and its urea **(7a–f)**, sulfonamide **(9a–d)** and acetamide **(12a–d)** derivatives were synthesized and were characterized by ^{1}H NMR, ^{13}C NMR and LC–MS analysis and were screened for their antimicrobial activities. The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and LC–MS analysis. All compounds were evaluated for *in vitro* antibacterial activities against *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 442) strains and *in vitro* antifungal activities against *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) strains by using serial broth dilution method. These compounds showed good antimicrobial activities against above bacterial species.

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1. Introduction

For many years rising antibiotic resistance of bacterial pathogens has been observed in both the Gram-positive and Gram-negative bacteria. In fact, introducing chloroquine into treatment of malaria more than 60 years ago triggered a new era of rapidly developing antimicrobial drugs. To improve the potency and antibacterial spectrum of existing drugs, many research groups have been put considerable efforts in this area (Sreeramulu et al., 2011; Salman et al., 2015; Sreeramulu and Ashokgajapathiraju, 2014; Bukvic et al., 2009). A key goal, however, is that of finding new chemical entries rather than enduring the search for new member of previously defined chemical classes (Xu et al., 2009; Kabir et al., 2008; Hirokawa et al., 2008; Aridoss et al., 2008). The nitrogen-containing heterocycles have always constituted a subject of immense interest due to their ubiquity in nature and well-known presence as a part of skeletal backbone of several therapeutic agents. Some of the indole based entities (Saundane et al., 2013; Paudel et al., 2012; Yang et al., 2012; Youngsaye et al., 2012; Jiang et al., 2012; El-Sayed et al., 2011; Zoraghi et al., 2011; Kamaria et al., 2011; Tomkiewicz et al., 2010; Damodiran et al., 2009; Samsoniya et al., 2009; Wang et al., 2000; Cirrincione et al., 1999; Hishmat et al., 1988) are reported for their antimicrobial activities. Moreover, in synthetic medicinal chemistry the pyrazino[1,2-*a*]indoles motif is widely exploited revealing a spectrum of important biological activities such as serotonin antagonist (Ruppelt et al., 1999), thrombolytic (McCort et al., 1998) in cardiovascular diseases (McCort et al., 1998), antidepressant, anxiolytic (Commons et al., 1996), central nervous system depressants (Freed, 1977), anticonvulsants (Mokrosz et al., 1994), antihistaminic (Basanagoudar et al., 1991; Rajur et al., 1989), protein kinase C inhibitors (Davis et al., 1991; Bit et al., 1993), 5-HT_{2A} (Fong et al., 2002), 5-HT_{2C} (Fong et al., 2002; Bos et al., 1997) and selective imidazoline I_2 receptor ligands (Glennon et al., 2004) and have been paid significant attention. Recently, the chemical entities containing pyrazino[1,2-*a*] indole nucleus

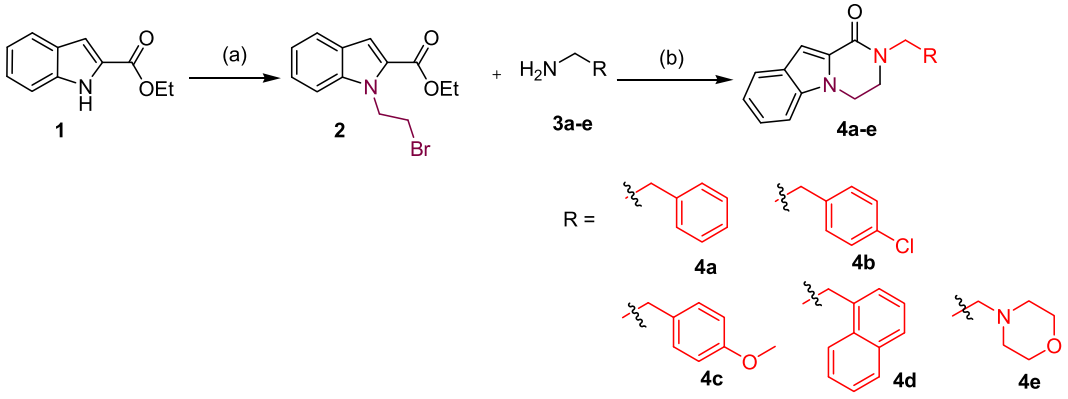
were identified as a novel potent antiproliferative agent against the human chronic myelogenous leukemia K562 cell line (Romagnoli et al., 2009).

On the other hand, literature survey revealed that some of the substituted 10-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles have possessed antifungal and antibacterial activities (Tiwari et al., 2006a, 2006b). Due to the exceeding biological importance of pyrazino[1,2-*a*]indoles nucleus, we aimed to examine new representatives of these tricyclic ring system based on a functionalized 3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one scaffold. The structures of synthesized compounds were assigned on the basis of ^{1}H NMR and ^{13}C NMR data. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi.

2. Chemistry

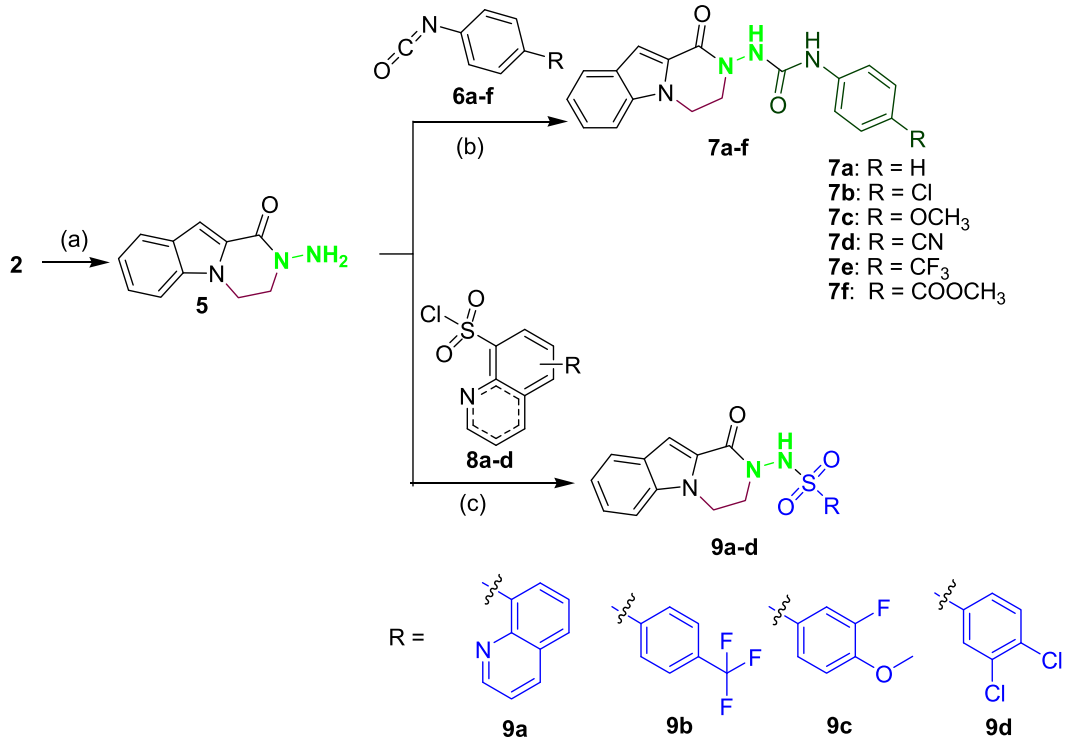
The synthetic route of compounds (**4a–e**), (**7a–f**), (**9a–d**) and (**12a–d**) is shown in Schemes 1–3 respectively.

The starting material ethyl 1-(2-bromoethyl)-1*H*-indole-2-carboxylate **2** was obtained by the coupling reaction of ethyl



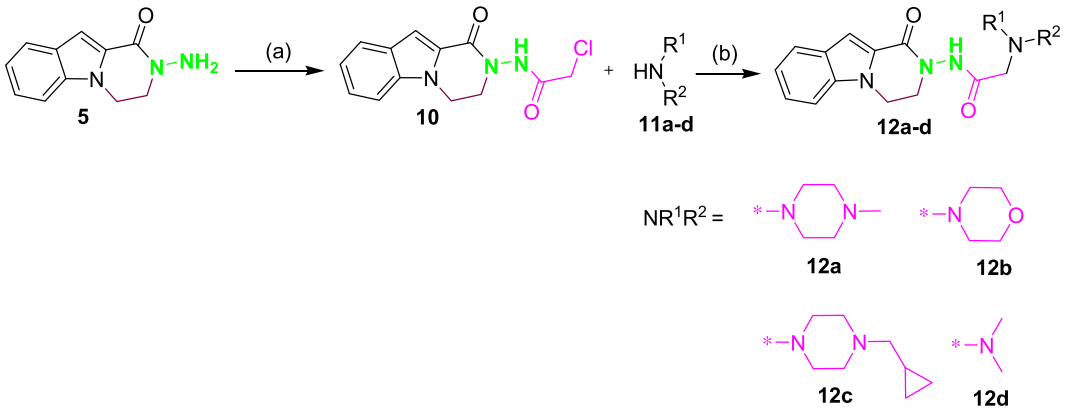
Reagents and conditions: **(a)** $Br(CH_2)_2Br$, K_2CO_3, Acetonitrile, 80°C **(b)** Acetonitrile, 60°C.

Scheme 1 Synthetic scheme for the title compounds **(4a–e)**.



Reagents and conditions: **(a)** $N_2H_4{\cdot}H_2O$, neat heat 80°C **(b)** Dichloromethane, rt. **(c)** Pyridine, Dichloromethane, rt.

Scheme 2 Synthetic scheme for the title compounds **(7a–f)** and **(9a–d)**.



Reagents and conditions: **(a)** Chloroacetic acid, EDC.HCl, DMAP, Dichloromethane, rt **(b)** Acetonitrile, 80°C.

Scheme 3 Synthetic scheme for the title compounds **(12a–d)**.

1*H*-indole-2-carboxylate **1** with 1,2-dibromoethane in the presence of K_2CO_3 as a base and acetonitrile as a solvent (Tapia et al., 2002). Subsequently, the cyclization reaction of ethyl 1-(2-bromoethyl)-1*H*-indole-2-carboxylate **2** and equimolar amounts of amines **(3a–e)** in acetonitrile provided 2-(substitu ted)-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **(4a–e)** respectively (Scheme 1).

The novel cyclized key intermediate 2-amino-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-one **5** was achieved by cyclocondensation reaction of hydrazine monohydrate with compound **2** at 80 °C. Further the compound **5** was used as key intermediate for the synthesis of compounds **(7a–f)**, **(9a–d)** and **(12a–d)** respectively. So the 1-(aryl)-3-(1-oxo-3,4-dihy dropyrazino[1,2-*a*]indol-1(2*H*)-yl)urea **(7a–f)** were synthesized by nucleophilic addition of compound **5** to equimolar amounts of aryl isocynates **(6a–f)** in dichloromethane at room temperature. Furthermore, the various (substituted)-*N*-(1-oxo-3,4-dihydropyrazino[1,2-*a*]indol-1(2*H*)-yl)aryl sulfonamide **(9a–d)** were synthesized by nucleophilic substitution reaction of aryl sulfonyl chlorides **(8a–d)** with compound **5** in the presence of pyridine as a base and dichloromethane as solvent at room temperature (Scheme 2).

On the other hand, the 2-(substituted)-*N*-(3,4-dihydro-1-oxopyrazino[1,2-*a*]indol-1(2*H*)-yl)acetamide **(12a–d)** were achieved *via* two step synthesis. In step first, the 2-chloro-*N*-(3,4-dihydro-1-oxopyrazino[1,2-*a*]indol-1(2*H*)-yl)acetamide **10** was obtained by coupling reaction of chloroacetic acid and compound **5** by using 1-(3-dimethylaminopropyl)-3-ethylcarbo diimide hydrochloride (EDC.HCl) in dichloromethane at room temperature. In the second step, the equimolar amounts of cyclic amines **(11a–d)** were condensed with 2-chloro-*N*-(3,4-dihydro-1-oxopyrazino[1,2-*a*]indol-1(2*H*)-yl)acetamide **10** afforded 2-(substituted)-*N*-(3,4-dihydro-1-oxopyrazino[1,2-*a*]indol-1(2*H*)-yl)acetamide **(12a–d)**.

3. Results and discussion

3.1. Analytical results

A series of four allied candidates **(4a–e)**, **(7a–f)**, **(9a–d)** and **(12a–d)** were synthesized substantially through the synthetic route as illustrated in Schemes 1–3. The off structure reaction products were confirmed by means of ^{1}H NMR and ^{13}C NMR spectra, e.g. ^{1}H NMR spectrum of compound **2** indicated the presence of two triplet signals appeared at δ 4.97–4.93 ppm and δ 3.82–3.76 ppm of adjoining CH_2 protons of bromoethyl group. The ^{13}C NMR spectra exhibited highest frequency signal at δ 165.78 ppm assignable to ester carbonyl, where as signals appeared around δ 31.71 and 52.84 ppm were assigned for two CH_2 of bromethyl carbons. Furthermore, the ^{1}H NMR spectrum of compound **(4a–e)** showed singlet for methylene proton at δ 4.74 ppm and aromatic protons resonate as multiplets at δ 6.90–7.68 ppm. The ^{13}C NMR spectrum is in well agreement with the structure assigned. In the ^{13}C NMR spectra, signals appeared around δ 43.18–48.64 ppm are assigned for methylene carbons whereas δ 121.13–136.76 ppm is attributed to aromatic carbons and carbonyl carbon was observed at about δ 159.20 ppm. The key intermediate **5** (Katritzky et al., 2003) was characterized by ^{1}H NMR spectrum which exhibited lack of the characteristic signal as quartet triplet pattern corresponding to the ethyl ester of compound **2** and the presence of broad singlet at δ 5.18 ppm NH_2 group (D_2O exchangeable). ^{13}C NMR spectra exhibited highest frequency signal at δ 158.14 ppm assignable to the pyrazino carbonyl carbon, whereas lowest frequency signal appears between 45.01 and 50.86 ppm for two CH_2 carbons of newly formed 3,4-dihydropyrazino ring in all the spectra. The ^{1}H NMR spectra of urea derivatives **(7a–f)** indicated the presence of two broad singlets appeared at around δ 9.54 ppm for NH proton attached to the pyrazino ring whereas other NH proton attached to aryl ring appeared at around δ 8.72 ppm. Moreover, disappearance of broad singlet at δ 5.18 ppm of NH_2 proton of compound **5** clearly confirmed the formation of urea derivatives. In ^{13}C NMR spectra of urea derivatives the most characteristic signal appears at δ 160.54 ppm for the carbonyl carbon between two NH groups of urea. Furthermore, the ^{1}H NMR spectrum of sulfonamide derivatives **(9a–d)** showed addition of aromatic multiplet and most downfield broad singlet appeared at around δ 10.05–11.02 ppm for sulfonamide NH proton. ^{13}C NMR spectra showed highest frequency signal range observed around δ 158.67 ppm assignable to the pyrazino carbonyl carbon. Finally, the ^{1}H NMR spectrum of

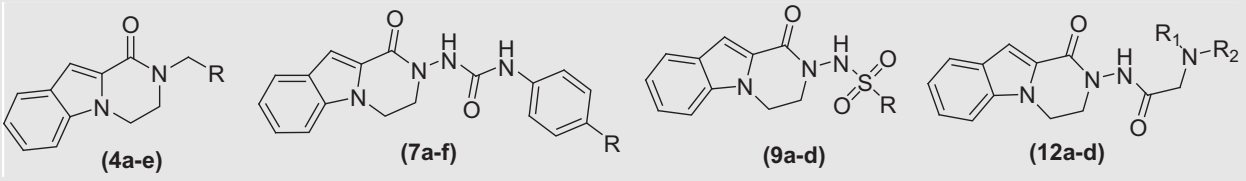
acetamide derivatives (**12a–d)** showed one downfield broad singlet signal appears at around δ 10.24 ppm corresponding to NH protons, whereas sharp singlet of amidic CH_2 protons observed at δ 3.08 ppm. ^{13}C NMR revealed the highest frequency signals at δ 168.83 ppm assigned for carbonyl carbon of amide function.

3.2. Antimicrobial activity results

The results of antimicrobial screening of newly prepared compounds were expressed as the MIC values are summarized in Table 1.

Many of newly synthesized compounds are found to exhibit good to excellent antimicrobial activity. From antimicrobial activity data (Tables 1 and 2), it is observed that compounds **4b** (R = 4-Cl–C_6H_4), **7b** (R = Cl), **9d** (R = 3,4-di-Cl–C_6H_3), **4e** (R = morpholine) and **12b** (R_1, R_2 = morpholine) are most active compounds. Data of antibacterial activity reveal that, compounds **4b** (R = 4-Cl–C_6H_5), **7f** (R = –COOMe), **9a** (quinoline-8-sulfonamide) and **9d** (R = 3,4-di-Cl–C_6H_3), are considered to be good active against *Escherichia coli*. When we have taken the morpholine group as substitution in compounds **4e** and **12b**, it shows excellent activity against *E. coli*. Compounds **4b** (R = 4-Cl–C_6H_4), **7b** (R = Cl), **7f** (R = COOMe) and **9d** (R = 3,4-di-Cl–C_6H_3) are considered as good active against *Pseudomonas aeruginosa*, while compounds **4e** (R = morpholine) and **12b** (R_1, R_2 = morpholine) are considered as very good active against *P. aeruginosa*. Compounds **4b** (R = 4-Cl–C_6H_4), **7b** (R = Cl), **7c** (R = OMe), and **9d** (R = 3,4-di-Cl–C_6H_3) are considered as good active against *Staphylococcus aureus*, while compounds **4e** (R = morpholine), **12b** (R_1, R_2 = morpholine) and **9a** (quinoline-8-sulfonamide) are considered as very good active against *S. aureus*. Compounds **4b** (R = 4-Cl–C_6H_4), **4e** (R = morpholine) and **9d** (R = 3,4-di-Cl–C_6H_3) are considered to be good active against *Streptococcus pyogenes*, while compound **12b** (R_1, R_2 = morpholine) is considered as very good active against *S. pyogenes*. For the antifungal activity, we have screened the same compounds which are used for antibacterial activity. Compounds **4b** (R = 4-Cl–C_6H_4), **4e** (R = morpholine), **9a** (quinoline-8-sulfonamide), **9b** (R = 4-OCF_3–C_6H_4) and **12a** (4-methyl piperazine) are considered as good active against *Candida albicans*, while compounds **4c** (R = 4-OCH_3–C_6H_5), **7b** (R = Cl), **7c** (R = OCH_3), **7d** (R = CN), **9d** (R = 3,4-di-Cl–C_6H_3) and **12b** (R_1, R_2 = morpholine) are considered as excellent active against *C. albicans*. Compounds **4e** and **12b** are considered as good active against *Aspergillus niger*. Only compound **12b** is good active against *Aspergillus clavatus* among the entire screened compounds. We have discussed and compared antibacterial and antifungal activities based on standard drugs ampicillin and griseofulvin, respectively.

Table 1 Results of antibacterial screening of compounds **4a–e**, 7**a–f**, **9a–d** and **12a–d**.



Minimum Inhibitory Concentration (MIC) for bacteria (μg/mL)

Compound numbers	Gram-negative		Gram-positive	
	E.C. MTCC 443	P.A. MTCC 1688	S.A. MTCC 96	S.P. MTCC 442
4a	200	200	500	250
4b	100	100	250	100
4c	125	125	500	250
4d	500	250	500	500
4e	62.5	50	125	100
7a	200	200	500	200
7b	200	100	250	200
7c	125	200	250	500
7d	200	250	500	250
7e	200	125	500	500
7f	100	100	500	500
9a	100	200	125	250
9b	200	125	500	500
9c	500	200	500	125
9d	100	100	250	100
12a	250	125	500	125
12b	62.5	50	125	50
12c	500	250	500	500
12d	500	500	500	250
Ampi.	100	100	250	100

S.A., Staphylococcus aureus; S.P., Streptococcus pyogenes; E.C., *Escherichia coli*; P.A., Pseudomonas aeruginosa; MTCC, Microbial Type Culture Collection; Ampi., Ampicillin.

Table 2 Results of antifungal screening of compounds **4a–e**, 7**a–f**, **9a–d** and **12a–d**.

Minimum Inhibitory Concentration (MIC) for fungi (μg/mL)			
Compound numbers	C.A. MTCC 227	A.N. MTCC 282	A.C. MTCC 1323
4a	> 1000	250	250
4b	500	250	250
4c	250	1000	1000
4d	1000	500	500
4e	500	100	250
7a	> 1000	> 1000	> 1000
7b	250	500	500
7c	250	> 1000	> 1000
7d	250	500	500
7e	1000	1000	1000
7f	1000	> 1000	> 1000
9a	500	500	500
9b	500	500	500
9c	1000	250	500
9d	250	500	500
12a	500	> 1000	> 1000
12b	250	100	100
12c	1000	500	500
12d	1000	500	500
Grise.	500	100	100

C.A., *Candida albicans*; A.N., *Aspergillus* niger; A.C., *Aspergillus clavatus*; Grise., Griseofulvin.

3.3. Antimicrobial testing method

The MICs of synthesized compounds were carried out by broth microdilution method using DMSO as diluents to get desired concentration of compounds to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compound concentrations. The MIC was defined as the lowest concentration of the antibiotic or test sample allowing no visible growth. All the tubes showing no visible growth (same as control tube) were subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic, a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted obtaining 2000 μg/mL concentration as a stock solution. In primary screening 500, 250 and 200 μg/mL concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 100, 62.5, 50 and 25 μg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

4. Experimental

4.1. Materials and methods

All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C respectively using either $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts, δ, are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^{1}H NMR), and 77.3 (^{13}C NMR); DMSO-d_6, δ 2.50 (^{1}H NMR), and 40.2 (^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. All melting points have been determined on a manually operated Veego (VMP-1) melting point apparatus and are reported uncorrected.

*4.2. Synthesis of ethyl 1-(2-bromoethyl)-1H-indole-2-carboxylate (**2**)*

A mixture of 1,2-dibromo ethane (52.0 mmol, 4.5 mL), potassium carbonate (79.3 mmol, 10.9 g) and ethyl 1*H*-indole-2-carboxylate **1** (26.4 mmol, 5.0 g) in of acetonitrile (50 mL) was at reflux for 72 h. After cooling the reaction mixture the salt was filtered out and washed with (20 mL) acetonitrile. The residue was concentrated and purified by column chromatography with petroleum ether/ethyl acetate (6:1 to 3:1) as an eluent to give as viscous oil 2: Yield 65%; m.p. 155–158 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.70–7.66 (t, 2H, J = 7.5 Hz, ArH), 7.39–7.35 (m, 1H, ArH), 7.32 (s, 1H, indole), 7.17–7.12 (t, 1H, J = 7.8 Hz, ArH), 4.97–4.93 (t, 2H, J = 13.2 Hz), 4.36–4.29 (q, 2H, J = 6.8 Hz, ester), 3.82–3.76 (t, 2H, J = 6.6 Hz, CH_2Br), 1.36–1.31 (t, 3H, J = 3.6 Hz, ester) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 13.83, 31.71, 52.84, 61.34, 103.80, 117.27, 123.12, 125.52, 127.60, 131.71, 148.34, 147.20, 165.78 ppm.

*4.3. General procedure for the synthesis of 2-(substituted)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one **4a–e***

To a solution of ethyl 1-(2-bromoethyl)-1*H*-indole-2-carboxylate **2** (0.100 g, 0.169 mmol) in acetonitrile (10 mL) at room temperature appropriate amines **(3a–e)** (0.186 mmol) was added. The mixture was heated at 80 °C for 20 min. After cooling the reaction mixture was quenched with cold water. The formed solid was filtered and washed with water to give pure compound **4a–e** respectively.

*4.3.1. 2-Benzyl-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**4a**)*

White solid, (0.063 g), Yield, 68%; m.p. 130–132 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.70–7.67 (d, 1H, J = 8.1 Hz, ArH), 7.54–7.51 (d, 1H, J = 8.4 Hz, ArH), 7.44–7.39 (m, 5H, ArH), 7.33–7.28 (t, 1H, J = 7.8 Hz, ArH), 7.14 (s, 1H, indole CH), 7.11–7.09 (d, 1H, J = 5.1 Hz), 4.74 (s, 2H, benzylic CH_2), 4.36–4.32 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 3.78–3.74 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 45.02, 51.73, 106.60, 111.31, 113.91, 115.90, 116.18, 121.13, 122.69, 125.23, 126.23, 127.03, 128.44, 130.78, 136.76, 158.61 ppm. LC–MS: (277.3, 96.76%)

*4.3.2. 2-(4-Chlorobenzyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**4b**)*

White solid, Yield: 0.077 g, 74%; m.p. 202–204 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.70–7.67 (d, 1H, J = 7.8 Hz, ArH), 7.53–7.51 (d, 1H, J = 8.4 Hz), 7.39–7.27 (m, 5H, ArH), 7.14 (s, 1H, indole CH), 7.11–7.09 (d, 1H, J = 5.7 Hz, ArH), 4.75 (s, 2H, CH_2), 4.35–4.32 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 3.77–3.73 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 46.01, 48.74, 105.22, 111.14, 120.87, 122.50, 124.52, 127.17, 129.04, 129.04, 129.73, 129.73, 130.14, 132.36, 136.61, 136.91, 159.56 ppm. LC–MS: (311.1, 97.50%).

*4.3.3. 2-(4-Methoxybenzyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**4c**)*

Off white solid: Yield, 0.079 g, 77%; m.p. 177–180 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.69–7.66 (d, 1H, J = 7.8 Hz, ArH), 7.52–7.49 (d, 1H, J = 8.4 Hz, ArH), 7.31–7.27 (m, 3H, ArH), 7.13 (s, 1H, ArH, indole CH), 7.11–7.08 (t, 1H, J = 3.9 Hz, ArH), 6.93–6.90 (d, 2H, J = 8.4 Hz, ArH), 4.67 (s, 2H, benzylCH_2), 4.23–4.28 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 3.73 (s, 3H, OCH_3), 3.70–3.68 (t, 2H, J = 5.7 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 45.62, 48.64, 55.52, 105.05, 111.09, 114.45, 120.81, 122.44, 124.41, 127.16, 129.69, 129.90, 136.54, 159.03 ppm. LC–MS: (301.3, 97.53%).

*4.3.4. 2-((Naphthalen-1-yl)methyl)-3,4-dihydro-pyrazino[1,2-a]indol-1(2H)-one (**4d**)*

White solid: Yield, 0.076 g, 69%; m.p. 186–189 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.22–8.19 (d, 1H, J = 8.4 Hz, ArH), 7.99–7.91 (dd, 2H, J = 7.2 Hz, ArH), 7.71–7.69 (d, 1H, J = 8.1 Hz, ArH), 7.58–7.48 (m, 5H), 7.32–7.27 (t, 1H, J = 7.2 Hz, ArH), 7.17 (s, 1H, indole CH), 7.15–7.10 (t, 1H, J = 7.5 Hz, ArH), 5.23 (s, 2H, benzyl CH_2), 4.27–4.25 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 3.74–3.71 (t, 2H, J = 5.7 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 45.38, 47.08, 105.36, 111.14, 120.90, 122.51, 123.99, 124.53, 126.00, 127.01, 127.21, 128.67, 129.16, 131.59, 132.87, 133.99, 136.59, 159.35 ppm. LC–MS: (327.2, 97.25%).

*4.3.5. 2-(2-Morpholinoethyl)-3,4-dihydro-pyrazino[1,2-a]indol-1(2H)-one (**4e**)*

White solid: Yield, 0.075 g, 75%; m.p. 161–163 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.68–7.65 (d, 1H, J = 8.1 Hz, ArH), 7.55–7.52 (d, 1H, J = 8.4 Hz, ArH), 7.32–7.27 (t, 1H, J = 8.1 Hz, ArH), 7.13–7.08 (t, 1H, J = 7.8 Hz, ArH), 7.03 (s, 1H, indole CH), 4.35–4.31 (t, 2H, J = 5.4 Hz, ArH), 3.88–3.84 (t, 2H, J = 6.0 Hz, morpholin CH_2), 3.66–3.62 (t, 2H, J = 6.3 Hz, NCH_2CH_2N), 3.56–3.53 (t, 4H, J = 4.5 Hz, NCH_2-CH_2N), 2.55–2.51 (m, 2H, morpholin CH_2), 2.49–2.43 (m, 2H, morpholin CH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.18, 46.58, 53.80, 53.80, 56.20, 66.77, 66.77, 104.64, 111.10, 120.76, 122.40, 124.29, 127.15, 130.11, 136.46, 159.20 ppm. LC–MS: (300.2, 99%).

*4.4. Synthesis of 2-amino-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (**5**)*

Mixture of hydrazine monohydrate (1.69 mmol, 0.084 g) and compound **2** (0.169 mmol, 0.050 g) was heated at 80 °C for 30 min (TLC check). After cooling the reaction mixture to room temperature, the solid precipitated was filtered and washed with excess of water to get colorless solid; Yield, 0.042 g, 75%; m.p. 234–238 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.68–7.65 (d, 1H, J = 8.1 Hz, ArH), 7.54–7.51 (d, 1H, J = 8.1 Hz, ArH), 7.32–7.27 (m, 1H, ArH),7.31–7.08 (m, 1H, ArH), 7.04 (s, 1H, indole CH), 5.18 (br.s, 2H, NH_2, D_2O-exchangable), 4.40–4.38 (t, 2H, J = 6.0 Hz, NCH_2CH_2N), 3.91–3.87 (t, 2H, J = 6.3 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 49.74, 104.46, 111.05, 120.77, 122.38, 124.35, 127.39, 129.87, 136.63, 158.64 ppm. LC–MS: (202.2, 94.95%).

*4.5. General procedure for the synthesis of 1-(aryl)-3-(1-Oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)urea **7a–f***

To a solution of compound **5** (0.100 g, 0.248 mmol) in dry dichloromethane (10 mL) at room temperature was added the substituted aromatic isocyanates **(6a–f)** (0.273 mmol). The reaction mixture was stirred at room temperature overnight. The obtained solid was filtered and washed with 10 mL of chloroform to get pure product.

*4.5.1. 1-(Phenyl)-3-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)urea (**7a**)*

White solid: Yield 0.119 g, 75%; m.p 167–169 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.00 (br.s, 1H, aromatic NH), 8.62 (br.s, 1H, pyrazino NH), 7.72–7.69 (d, 1H, J = 8.1 Hz, ArH), 7.59–7.56 (d, 1H, J = 8.7 Hz), 7.49–7.47 (d, 2H, J = 7.5 Hz, ArH), 7.37–7.32 (t, 1H, J = 7.5 Hz, ArH), 7.29–7.24 (t, 1H, J = 7.5 Hz, ArH), 7.17–7.12 (m, 2H, ArH), 7.00–6.98 (m, 2H, ArH), 4.50–4.53 (t, 2H, J = 5.3 Hz, NCH_2-CH_2N), 4.04–3.98 (t, 2H, J = 5.1 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.94, 105.93, 111.29, 119.10, 120.98, 122.61, 122.61, 122.61, 124.89, 127.19, 129.13, 129.13, 129.13, 129.71, 136.74, 139.88, 155.23, 160.14 ppm. LC–MS: (321.2, 97.54%).

*4.5.2. 1-(4-Chlorophenyl)-3-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)urea (**7b**)*

White solid: Yield, 0.125 g, 71.5%; m.p. 197–199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.15 (br.s, 1H, aromatic NH) 8.72 (br.s, 1H, Pyrazino NH), 7.72–7.69 (d, 1H, J = 8.1 Hz, ArH), 7.59–7.51 (m, 3H, ArH), 7.37–7.30 (m, 3H, ArH), 7.17 (s, 1H, indole CH), 7.14–7.03 (m, 1H, ArH), 4.52–4.49 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 4.05–4.01 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.90, 105.98, 111.29, 120.68, 121.00, 122.62, 124.92, 126.15, 127.18, 128.97, 128.97, 128.97, 129.67, 136.74, 138.94, 155.13, 160.19 ppm. LC–MS: (355.2, 93.12%).

*4.5.3. 1-(4-Methoxyphenyl)-3-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)urea (**7c**)*

White solid: Yield, 0.125 g, 72%; m.p. 245–248 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.82 (br.s, 1H, aromatic NH), 8.53 (br.s, 1H, pyrazino NH), 7.72–7.69 (d, 1H, J = 7.8 Hz, ArH), 7.59–7.56 (d, 1H, J = 8.4 Hz, ArH), 7.39–7.35 (m, 3H, ArH), 7.16 (s, 1H, indole CH), 7.14–7.15 (m, 1H, ArH), 6.87–6.84 (d, 2H, J = 9.0 Hz, ArH), 4.52–4.48 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 4.05–4.01 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 3.71 (s, 3H, OCH_3) ppm. ^{13}C NMR (75 MHz,

DMSO-d_6) δ: 50.97, 55.59, 105.87, 111.27, 114.29, 114.29, 120.96, 120.96, 122.60, 124.87, 127.19, 129.76, 132.85, 136.72, 155.09, 155.43, 160.19 ppm. LC–MS: (351.2, 99.9%).

*4.5.4. 1-(4-Cyanophenyl)-3-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)urea (**7d**)*

White solid: Yield, 0.120 g, 70%; m.p. 241–243 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.54 (br.s, 1H, aromatic NH), 8.92 (br.s, 1H, pyrazino NH), 7.75–7.67 (m, 5H, ArH), 7.59–7.57 (d, 1H, J = 8.1 Hz), 7.37–7.32 (t, 1H, J = 7.2 Hz, ArH), 7.18 (s, 1H, indole CH), 7.14–7.12 (d, 1H, J = 7.5 Hz, ArH), 4.53–4.51 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 4.06–4.02 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.82, 50.82, 104.10, 106.10, 111.31, 118.93, 119.71, 121.02, 122.64, 124.97, 127.17, 129.55, 133.65, 133.65, 133.35, 136.76, 144.48, 154.79, 160.11 ppm. LC–MS: (346.3, 98%).

*4.5.5. 1-(4-(Trifluoromethyl)phenyl)-3-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)urea (**7e**)*

Off white solid: Yield, 0.129 g, 67%; m.p. 282–285 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.44 (br.s, 1H, aromatic NH), 8.85 (br.s, 1H, pyrazino NH), 7.73–7.70 (m, 3H, ArH), 7.65–7.62 (d, 2H, J = 9.0 Hz, ArH), 7.59–7.56 (d, 1H, J = 8.4 Hz, ArH), 7.37–732 (t, 1H, J = 7.5 Hz, ArH), 7.18 (s, 1H, indole CH), 7.17–7.12 (t, 1H, J = 7.5 Hz, ArH), 4.53–4.49 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 4.07–4.03 (t, 2H, J = 6.0 Hz, ArH, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.86, 50.86, 106.05, 111.31, 118.78, 121.01, 122.33, 122.64, 122.73, 123.20, 124.95, 126.43, 126.80, 127.17, 129.60, 136.76, 143.72, 154.98, 160.15 ppm. LC–MS: (389.1, 96.25%).

*4.5.6. Methyl 4-(3-(1-Oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)ureido)benzoate (**7f**)*

White crystals: Yield, 0.131 g, 70%; m.p. 278–280 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.43 (br.s, 1H, aromatic NH), 8.83 (br.s, 1H, pyrazino NH), 7.90–7.87 (d, 2H, J = 8.4 Hz, ArH), 7.72–7.57 (m, 4H, ArH), 7.38–7.33 (t, 1H, J = 7.2 Hz, ArH), 7.18 (s, 1H, indole CH), 7.14–7.12 (d, 1H, J = 7.2 Hz, ArH), 4.51–4.49 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 4.06–4.04 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 3.81 (s, 3H, $COOCH_3$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.85, 50.25, 106.05, 111.31, 118.25, 121.01, 122.63, 123.23, 124.95, 127.17, 129.59, 130.74, 130.74, 136.75, 144.89, 154.89, 166.57 ppm. LC–MS: (379.3, 96.76%).

*4.6. General procedure for the synthesis of substituted-N-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)aryl sulfonamide **9a–d***

To a solution of compound **5** (0.100 g, 0.248 mmol) in dichloromethane (10 mL) at room temperature was added appropriate aromatic sulfonyl chloride **8a–d** (0.248 mmol) and pyridine (0.497 mmol). The reaction mixture was stirred at room temperature for 4–5 h and then diluted with water (25 mL). The product was extracted with dichloromethane (3 × 20 mL); the extract was washed with dilute citric acid (20 mL, pH = 7.8). The organic layer was dried over sodium sulfate and evaporated under reduced pressure to obtain pure compound.

*4.6.1. N-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl) quinoline-8-sulfonamide (**9a**)*

Off white solid: Yield, 0.128 g, 66%; m.p. 210–212 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.05 (br.s, 1H, sulfonamide NH), 9.09–9.07 (dd, 1H, J = 1.5 Hz, ArH), 8.59–8.55 (dd, 1H, J = 1.8 Hz), 8.33–7.71 (m, 3H, ArH), 7.69–7.67 (m, 1H, ArH), 7.60–7.57 (d, 1H, J = 8.1 Hz), 7.53–7.50 (d, 1H, J = 8.4 Hz), 7.34–7.29 (m, 1H, ArH), 7.14–7.06 (m, 1H, ArH), 6.86 (s, 1H, indole CH), 4.47–4.41 (t, 2H, J = 6.3 Hz, NCH_2CH_2N), 4.14–4.10 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 52.16, 52.16, 106.45, 111.28, 121.06, 122.59, 122.99, 125.15, 125.90, 126.95, 128.91, 130.82, 134.76, 136.66, 136.80, 137.41, 143.81, 143.81, 151.63, 158.78 ppm. LC–MS: (393.2, 97.19%).

*4.6.2. 4-(Trifluoromethoxy-N-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)benzene sulfonamide (**9b**)*

White solid: Yield, 0.164 g, 81%; m.p. 233–238 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.01 (br.s, 1H, sulfonamide NH), 7.95–7.92 (d, 2H, J = 8.4 Hz, ArH), 7.81–7.78 (d, 1H, J = 8.1 Hz, ArH), 7.71–7.68 (d, 1H, J = 8.1 Hz, ArH), 7.66–7.63 (d, 1H, J = 7.3 Hz, ArH), 7.56–7.54 (d, 1H, J = 8.1 Hz, ArH), 7.37–7.32 (t, 1H, J = 7.5 Hz, ArH), 7.14–7.09 (t, 1H, J = 7.8 Hz, ArH), 7.02 (s, 1H, indole CH), 4.49–4.43 (t, 2H, J = 6.3 Hz, NCH_2CH_2N), 4.10–4.06 (t, 2H, J = 6.0 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.95, 106.68, 111.31, 121.13, 122.68, 125.28, 126.59, 126.79, 126.99, 127.50, 128.31, 129.03, 129.27, 136.77, 142.91, 143.37, 146.08, 152.63, 158.70 ppm. LC–MS: (410.1, 96.25%).

*4.6.3. Fluoro-4-methoxy-N-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl) benzene sulfonamide (**9c**)*

Colorless solid: Yield, 0.164 g, 85%; m.p. 182–184 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.63 (br.s, 1H, sulfonamide NH), 7.71–7.64 (m, 3H, ArH), 7.56–7.53 (d, 1H, J = 8.4 Hz, ArH), 7.37–7.25 (m, 2H, ArH), 7.15–7.10 (m, 1H, ArH), 7.04 (s, 1H, indole CH), 4.49–4.46 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 4.07–4.4.03 (t, 2H, J = 5.1 Hz, NCH_2CH_2N), 3.90 (s, 3H, OCH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 43.12, 51.90, 106.71, 111.32, 117.97, 118.26, 121.12, 122.68, 125.27, 126.99, 128.31, 129.83, 129.95, 130.79, 136.78, 158.67, 171.72, 174.97 ppm. LC–MS: (390.2, 96.25%).

*4.6.4. 3,4-Dichloro-N-(1-oxo-3,4-dihydropyrazino[1,2-a]indol-1(2H)-yl)benzene sulfonamide (**9d**)*

Colorless solid: Yield, 0.171 g, 84%; m.p. 197–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.02 (br.s, 1H, sulfonamide NH), 8.08 (s, 1H, ArH), 7.86–7.77 (m, 2H, ArH), 7.66–7.64 (d, 1H, J = 8.1 Hz, ArH), 7.57–7.54 (d. 1H, J = 8.1 Hz, ArH), 7.37–7.32 (t, 1H, J = 7.8 Hz, ArH), 7.15–7.10 (t. 1H, J = 7.5 Hz, ArH), 7.06 (s, 1H, indole CH), 4.49–4.51 (t, 2H, J = 5.3 Hz, NCH_2CH_2N), 4.10–4.08 (t, 2H, J = 5.2 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.97, 106.76, 111.33, 121.13, 122.69, 125.28, 126.98, 128.44, 129.90, 131.75, 132.30, 136.80, 139.75, 158.71 ppm. LC–MS: (410.1, 411.0, 412.1, 96.25%).

*4.7. Synthesis of 2-chloro-N-(3,4-dihydro-1-oxopyrazino[1,2-a] indol-1(2H)-yl)acetamide (**10**)*

In compound **5** (0.994 mmol, 0.200 g) chloroacetic acid (1.044 mmol, 0.099 g) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.193 mmol, 0.299 g) were added in (10 mL) of dichloromethane and the reaction mixture was stirred for 10–15 min. The solid was filtered and washed with water, dried and recrystallized in ethyl acetate to get white solid, Yield, 0.198 g, 72%; m.p. 256–258 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.83 (br.s, 1H, pyrazino NH), 7.72–7.69 (d, 1H, J = 8.1 Hz, ArH), 7.58–7.55 (d, 1H, J = 8.1 Hz, ArH), 7.37–7.32 (t, 1H, J = 7.8 Hz, ArH), 7.18 (s, 1H, indole NH), 7.14–7.12 (d, 1H, J = 7.2 Hz, ArH), 4.49–4.45 (t, 2H, J = 5.7 Hz, NCH_2CH_2N), 4.24 (s, 2H, CH_2-Cl), 4.01–3.97 (t, 2H, J = 5.4 Hz, NCH_2CH_2N) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 49.88, 106.34, 111.35, 121.07, 122.66, 125.05, 127.12, 129.12, 136.79, 158.85, 165.68 ppm. LC–MS: (278.1, 98.04%).

*4.8. General procedure for the synthesis of N-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)-2-(substituted)acetamide (**12a–d**)*

To a solution of compound **10** (0.180 mmol) in acetonitrile (5 mL) respective amines **11a–d** (0.190 mmol) was added and the solution stirred for 1 h in the seal vial at 80 °C. Water was added in the mixture and the solid residue was filtered and dried to give pure **12a–d** respectively.

*4.8.1. N-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)-2-(4-methylpiperazin-1-yl)acetamide (**12a**)*

White solid: Yield, 0.096 g, 78%; m.p. 185–187 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.14 (br.s, 1H, pyrazino NH), 7.71–7.68 (d, 1H, J = 8.1 Hz, ArH), 7.57–7.54 (d, 1H, J = 8.4 Hz, ArH), 7.36–7.31 (t, 1H, J = 8.1 Hz, ArH), 7.16–7.14 (m, 1H, ArH), 7.11 (s, 1H, indole CH), 4.47–4.43 (t, 2H, J = 6.0 Hz, NCH_2CH_2N), 3.98–3.94 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 3.08 (s, 2H, amedic CH_2), 2.54–2.50 (m, 4H), 2.40 (m, 4H), 2.18 (s, 3H, N–CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 46.14, 50.12, 53.08, 53.08, 54.10, 54.90, 60.34, 106.03, 111.32, 212.01, 122.61, 124.91, 127.14, 129.44, 136.74, 158.90, 168.83 ppm. LC–MS: (342.3, 98.21%).

*4.8.2. N-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)-2-morpholinoacetamide (**12b**)*

White solid: Yield, 0.087 g, 74%; m.p. 210–212 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.24 (br.s, 1H, amide NH), 7.71–7.68 (d, 1H, J = 7.8 Hz, ArH), 7.57–7.54 (d, 1H, J = 8.4 Hz, ArH), 7.36–7.31 (d, 1H, J = 7.8 Hz, ArH), 7.16–7.11 (m, 2H, ArH), 4.47–4.43 (t, 2H, J = 5.4 Hz, NCH_2CH_2N) 3.99–3.95 (t, 2H, J = 6.0 Hz, NCH_2CH_2N), 3.77–3.74 (t, 2H, J = 4.8 Hz), 3.65–3.62 (t, 2H, J = 4.2 Hz), 3.10 (s, 2H, amedic CH_2), 3.07–3.03 (t, 2H, J = 5.1 Hz), 2.53–2.50 (t, 2H, J = 8.7 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 50.13, 53.65, 53.65, 60.64, 63.86, 63.86, 66.49, 66.49, 106.06, 111.33, 121.02, 122.61, 124.93, 127.13, 129.41, 136.74, 158.92, 168.71 ppm. LC–MS: (329.3, 97.16%).

*4.8.3. N-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)-2-(4-(cyclopropylmethyl) piperazin-1-yl)acetamide (**12c**)*

White solid: Yield, 0.101 g, 74%; m.p. 188–190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.12 (br.s, 1H, pyrazino NH), 7.71–7.68 (d, 1H, J = 8.1 Hz, ArH), 7.57–7.54 (d, 1H, J = 8.4 Hz, ArH), 7.36–7.31 (t, 1H, J = 7.2 Hz, ArH), 7.10–7.14 (m, 2H, ArH), 4.44–4.41 (t, 2H, J = 5.1 Hz, NCH_2CH_2N), 3.96–4.00 (t, 2H, J = 6.0 Hz, NCH_2CH_2N), 3.08 (s, 2H, amedic CH_2), 2.43–2.69 (m, 8H, piprazine), 2.18–2.16 (d, 2H, J = 6.6 Hz), 0.819 (m, 1H, cyclopropyl CH), 0.46–0.44 (d, 2H, J = 7.2 Hz), 0.072–0.059 (d, 2H, J = 3.9 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 4.18, 4.18, 8.75, 50.12, 52.98, 52.98, 53.33, 53.33, 60.54, 63.36, 106.02, 111.33, 121.02, 122.61, 124.91, 127.14, 129.45, 136.74, 158.91, 168.87 ppm. LC–MS: (382.3, 96.81%).

*4.8.4. N-(3,4-dihydro-1-oxopyrazino[1,2-a]indol-1(2H)-yl)-2-(dimethylamino)acetamide (**12d**)*

White solid: Yield, 0.072 g, 70%; m.p. 201–203 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.23 (br.s, 1H, pyrazino NH), 7.71–7.68 (d, 1H, J = 8.1 Hz, ArH), 7.53–7.54 (d, 1H, J = 8.4 Hz, ArH), 7.36–7.31 (t, 1H, J = 7.1 Hz, ArH), 7.16–7.11 (t, 2H, J = 6.9 Hz, ArH), 4.46–4.42 (t, 2H, J = 5.4 Hz, NCH_2CH_2N), 3.98–3.94 (t, 2H, J = 6.0 Hz, NCH_2CH_2N), 3.03 (s, 2H, amedic CH_2), 2.29 (s, 6H, $N(CH_3)_2$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 45.90, 45.90, 50.12, 61.80, 106.02, 111.31, 121.0, 122.60, 124.90, 127.14, 129.48, 136.73, 158.90, 169.11 ppm. LC–MS: (287.2, 99%).

5. Conclusion

The new synthesized compounds exhibited promising antibacterial activity against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes strains*, while antifungal activity against *C. albicans*, *A. niger*, and *A. clavatus* strains. Compounds **4e** and **12b** possess excellent activity against both bacterial and fungal species. It is observed that introduction of morpholine group significantly enhances the microbial activity against both bacterial and fungal species.

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