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Synthesis and Antimicrobial Activity of Some New Formazan Derivatives

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Abstract: A series of new substituted formazan derivatives has been synthesized from corresponding aryl diazonium chloride and Schiff base in pyridine. The synthesized compounds were identified by spectral studies and screened for their antimicrobial activities.

Keywords: Schiff base, Formazan, Antimicrobial activity.

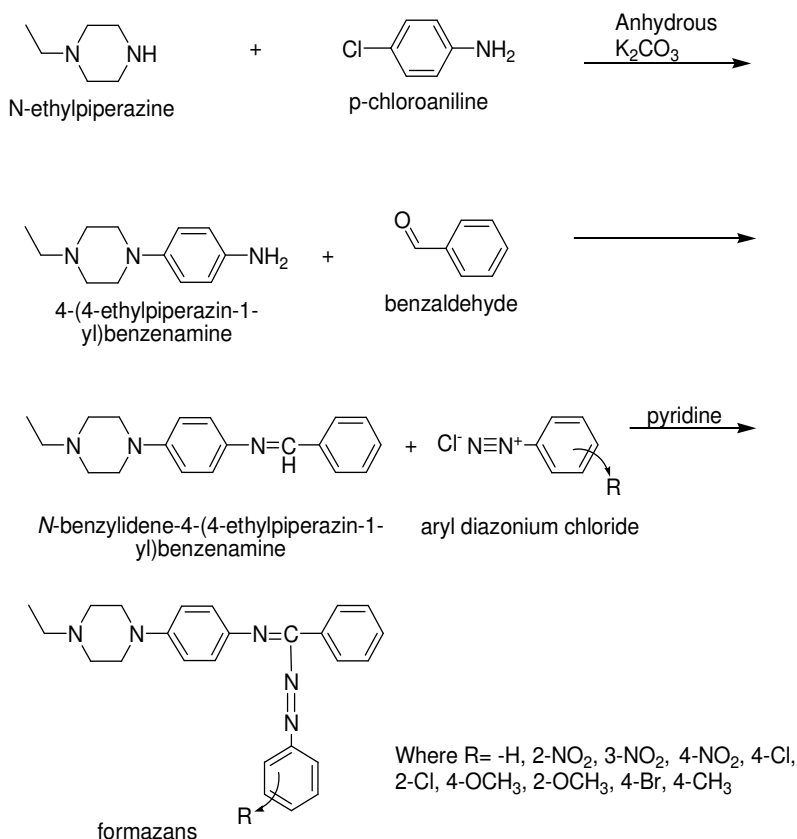
Introduction

Formazans have been found to possess important medical applications; the tetrazolium salts are classified as promoter of vitality formazans and heterocyclic hydrazones are known for their spectrum of biological activities such as antiviral^{1,2}, antimicrobial³, anti-inflammatory⁴, antifungal⁵, anticancer⁶, anti-HIV⁷⁻⁸, etc. Several formazans show promising anti-fertility⁹ and anti-parkinsonian activity¹⁰⁻¹³.

Piperazine derivatives have also shown to possess diverse biological properties such as anti-histamine, antikatonic, anticonvulsant, antibacterial¹⁴ and as potential cocaine-abuse therapeutic agents¹⁵. Piperazine possesses dopamine receptor activating property. The two nitrogen of the piperazine molecule are present in a rigid conformational structure that probably favours their involvement to the dopamine receptors¹⁶. In the present study we have synthesized ten substituted formazan derivatives (**3a-j**) by coupling Schiff base with appropriate aryl diazonium chlorides in pyridine. (Scheme 1) The structures of these derivatives were assigned on the basis of elemental analysis, IR and ¹H NMR spectral data. The synthesized compounds were screened for their antimicrobial activities.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8400S FTIR spectrophotometer. ^1H NMR spectra were recorded on a Hitachi 300MHz using TMS as an internal standard and elemental analysis had been carried out on Perkin-Elmer CHNS-2400.



Scheme 1.

General procedure for the preparation of formazans

Preparation of 4-(4-ethylpiperazin-1-yl) benzenamine (1)

A mixture of *N*-ethylpiperazine (0.1 mol) and *p*-chloroaniline (0.1 mol) and anhydrous K_2CO_3 in absolute alcohol (20 mL) was refluxed for 4 h. The resultant mixture was cooled to room temperature and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol.

Preparation of N-benzylidene-4-(4-ethylpiperazin-1-yl) benzenamine (2)

A mixture of 4-(4-ethylpiperazin-1-yl) benzenamine (0.1 mol) and benzaldehyde (0.1 mol) in absolute alcohol (20 mL) was refluxed for 2 h. After the completion of reaction it was poured into ice-cold water with stirring. The solid product obtained was filtered, washed with water and recrystallized from ethanol.

Preparation of N-(Substituted phenylimino)-N'-(4-(4-ethylpiperazin-1-yl) phenyl) benzamidine (Formazans) (3a-j)

A cold stirred solution of aniline (0.01 mol) previously dissolved in aqueous HCl (10 mL) was diazotized over crushed ice by dropwise addition of cold aqueous solution of NaNO₂ (2.5 g) with stirring till a clear solution of diazonium salt of respective amine was obtained. The temperature¹⁷ was at 0-5 °C. It was further stirred until the positive test of nitrous acid on starch-iodide paper was obtained. This mixture was then poured into a cold solution of *N*-Benzylidene-4-(4-ethylpiperazin-1-yl) benzenamine (0.01 mol) dissolved in dry pyridine (5.0 mL). The reaction mixture was further stirred for 2 h maintaining temperature 0-5 °C. The mixture was then poured into water with continuous stirring. The resultant dark coloured mass was filtered and washed with water till free from pyridine, dried and recrystallized from ethanol.

The spectral data of the synthesized compounds **3a-j** are given below.

N'-(4-(4-Ethylpiperazin-1-yl)phenyl)-N-(phenylimino)benzamidine (3a)

Yield 70%, m.p. 47 °C. IR (ν, cm⁻¹) (KBr): 1610, 1520, 1450, 1390, 1250; ¹H NMR (DMSO): δ 1.13 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.56-3.52 (t, 8H, piperazine), 6.6-7.3 (m, 14H, Ar-H); Anal. Calcd for C₂₅H₂₇N₅: C, 75.57, H, 6.80, N, 17.62%. Found C, 75.60, H, 6.83, N, 17.61%.

N-(2-Nitrophenylimino)-N'-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (3b)

Yield 65%, m.p. 130 °C. IR (ν, cm⁻¹) (KBr): 1610, 1580, 1500, 1460, 1390, 1320, 1280, 850; ¹H NMR (DMSO): δ 1.1 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.59-3.45 (t, 8H, piperazine), 6.6-8.2 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₆O₂: C, 67.89, H, 5.88, N, 19.0%. Found C, 67.85, H, 5.87, N, 19.02%

N-(3-Nitrophenylimino)-N'-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (3c)

Yield 65%, m.p. 63 °C. IR (ν, cm⁻¹) (KBr): 1625, 1580, 1495, 1450, 1390, 1300, 1191, 820; ¹H NMR (DMSO): δ 1.0 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.59-3.45 (t, 8H, piperazine), 6.5-8.1 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₆O₂: C, 67.89, H, 5.88, N, 19.0%. Found C, 67.94, H, 5.87, N, 19.01%

N-(4-Nitrophenylimino)-N'-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (3d)

Yield 70%, m.p. 127 °C. IR (ν, cm⁻¹) (KBr): 1620, 1540, 1500, 1460, 1350, 1300, 1250, 1191, 850; ¹H NMR (DMSO): δ 1.0 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.59-3.45 (t, 8H, piperazine), 6.6-8.2 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₆O₂: C, 67.89, H, 5.88, N, 19.0%. Found C, 67.95, H, 5.89, N, 18.99%

N-(4-Chlorophenylimino)-N'-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (3e)

Yield 75%, m.p. 76 °C. IR (ν, cm⁻¹) (KBr): 1625, 1600, 1484, 1380, 1300, 1243, 1089, 852; ¹H NMR (DMSO): δ 1.1 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.56-3.42 (t, 8H, piperazine), 6.5-7.4 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₅Cl: C, 69.54, H, 6.02, N, 16.21%. Found C, 69.60, H, 6.01, N, 16.22%

N-(2-Chlorophenylimino)-N'-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (3f)

Yield 75%, m.p. 99 °C. IR (ν, cm⁻¹) (KBr): 1620, 1590, 1490, 1400, 1230, 1090, 851; ¹H NMR (DMSO): δ 1.1 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.54-3.45 (t, 8H, piperazine), 6.5-7.3 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₅Cl: C, 69.54, H, 6.02, N, 16.21%. Found C, 69.50, H, 6.04, N, 16.20%

N-(4-Methoxyphenylimino)-*N'*-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (**3g**)

Yield 80%, m.p. 93 °C. IR (v, cm⁻¹) (KBr): 1620, 1580, 1450, 1400, 1310, 1172, 1085; ¹H NMR (DMSO): δ 1.0 (t, 3H, -CH₃), 2.3 (q, 2H, -CH₂), 2.59-3.45 (t, 8H, piperazine), 3.78 (s, 3H, -OCH₃), 6.5-7.4 (m, 13H, Ar-H); Anal. Calcd for C₂₆H₂₉N₅O: C, 73.07, H, 6.79, N, 16.38%. Found C, 73.01, H, 6.78, N, 16.35%

N-(2-Methoxyphenylimino)-*N'*-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (**3h**)

Yield 75%, m.p. 80 °C. IR (v, cm⁻¹) (KBr): 1620, 1570, 1450, 1370, 1305, 1175, 1085; ¹H NMR (DMSO): δ 1.1 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.56-3.40 (t, 8H, piperazine), 3.73 (s, 3H, -OCH₃), 6.4-7.3 (m, 13H, Ar-H); Anal. Calcd for C₂₆H₂₉N₅O: C, 73.07, H, 6.79, N, 16.38%. Found C, 73.02, H, 6.80, N, 16.40%

N-(4-Bromophenylimino)-*N'*-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (**3i**)

Yield 65%, m.p. 72 °C. IR (v, cm⁻¹) (KBr): 1630, 1595, 1490, 1380, 1240, ¹H NMR (DMSO): δ 1.0 (t, 3H, -CH₃), 2.4 (q, 2H, -CH₂), 2.59-3.46 (t, 8H, piperazine), 6.3-7.4 (m, 13H, Ar-H); Anal. Calcd for C₂₅H₂₆N₅Br: C, 63.05, H, 5.46, N, 14.70%. Found C, 63.0, H, 5.43, N, 14.67%

N-(4-Methylphenylimino)-*N'*-(4-(4-ethylpiperazin-1-yl)phenyl)benzamidine (**3j**)

Yield 70%, m.p. 82 °C. IR (v, cm⁻¹) (KBr): 1620, 1580, 1450, 1395, 1250, ¹H NMR (DMSO): δ 1.0 (t, 3H, -CH₃), 2.3 (s, 3H, -CH₃), 2.43 (q, 2H, -CH₂), 2.56-3.44 (t, 8H, piperazine), 6.6-7.6 (m, 13H, Ar-H); Anal. Calcd for C₂₆H₂₉N₅: C, 75.92, H, 7.05, N, 17.02%. Found C, 75.87, H, 7.08, N, 16.99%

Antimicrobial activity

The synthesized compounds **3a-3j** were screened for their antibacterial activity against *B. Subtilis*, *S. Typhi* and *E. Coli* and antifungal activity against *C. albicans* at a concentration of 40 µg/mL in DMF by cup-plate method^{18,19}. Standard anti-bacterial and antifungal drug, gentamycin and miconazole respectively were also tested under similar conditions for comparison. Zone of inhibition in mm of synthesized compounds and standard drugs are shown in Table 1.

Table 1. Antimicrobial activity of compounds (**3a-j**).

Compounds	<i>E. Coli</i>	<i>B. Subtilis</i>	<i>S. Typhi</i>	<i>C. Albicans</i>
3a	9.8	8.2	8.2	11
3b	7.8	-	7.8	13
3c	9.2	10	7.2	14
3d	10	7.4	-	13
3e	9.4	7.6	-	12
3f	12.8	8.6	9.8	13
3g	9.6	-	8.4	14
3h	9.2	-	8.0	11
3i	7.8	8.0	9.8	11
3j	9.4	-	10	12
Gentamycin	16.2	21.4	17.4	-
Miconazole	-	-	-	20

Conclusion

Most of the synthesized compounds have shown antibacterial activity to some extent. Among the synthesized compounds, compound **3f** shows good activity, while **3d**, **3a**, **3g**, **3e**, **3j**, **3c** and **3h** shows moderate activity. The other two compounds **3b** and **3i** show feeble activity against *E. coli*. Against *B. subtilis* the compound **3c** shows good activity, while compounds **3f**, **3a**, **3j**, **3e** and **3d** show moderate to feeble activity. The remaining compounds **3b**, **3i**, **3g** and **3h** have been found to be inactive against *B. subtilis*. The compound **3j** shows good activity, while compounds **3i**, **3f**, **3g**, **3a**, and **3h** show moderate activity against *S. typhi*. Compounds **3d** and **3e** have been found to be inactive against *S. typhi*. The compounds **3c** and **3g** show good activity while the remaining compounds **3b**, **3d**, **3f**, **3e**, **3j**, **3a**, **3i** and **3h** show moderate to good activity against *C. albicans*

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