Asian Journal of Chemistry; Vol. 24, No. 3 (2012), 1191-1194

ASIAN JOURNAL OF CHEMISTRY

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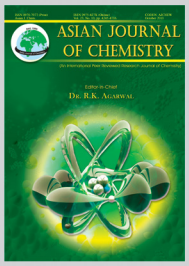

Synthesis of *N*-Methyl Benzenemethane Sulfonamide Substituted Carbazoles and Pyrazoles

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(*Received*: 5 March 2011; *Accepted*: 11 November 2011) AJC-10621

Cyclization of 1-(4-hydrazinophenyl)-*N*-methylmethanesulfonamide hydrochloride (**2**) with cyclohexanone (**3**)/*N*-methyl-4-piperidone (**5**) afforded the corresponding *N*-methyl-1-(2,3,4,9-tetrahydro-1H-carbazol-6-yl)methanesulfonamide (**4**) and *N*-methyl-1-(2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl)methane sulfonamide (**6**). Condensation of compound **2** with substituted aryl β-diketones gave the novel *N*-methyl-1-[4-(3-methyl-5-phenyl-1H-pyrazol-1-yl)phenyl]methanesulfonamide (**8**). All the synthesized compounds were characterized by their FT-IR, ^{1}H NMR and mass spectral data.

Key Words: Carbazoles, Pyrazoles, Sulfonamide derivatives, Cyclohexanone, *N*-Methylpiperidone.

INTRODUCTION

Carbazoles and pyrazole derivatives are very important class of organic compounds having wide range of biological activities[1-4] such as antibacterial[5,6], antifungal[7,8], antiinflammatory agents[9-12], anticancer and antiviral[13-18], antidepressant[19], insecticides and fungicides[20]. So it prompted us to prepare some new carbazole and pyrazole derivatives with a view to screen their biological activity. In this paper, the synthesis of some new carbazole and pyrazole derivatives bearing benzene methane sulfonamide substituents are reported.

EXPERIMENTAL

All the reagents used for reactions are of L.R. grade. Solvents were routinely distilled before use. IR spectra were recorded as KBr pellets on Thermo Nicolet Avatar 330 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 100 MHz Varian or 200 MHz Tecmag instruments using TMS as internal standard. Melting points are uncorrected and were determined in open capillaries on Mettler FP-90 apparatus. TLC was recorded on Merck silica gel 60 F254 plates and spots were detected using iodine chamber or UV lamp at 254 nm.

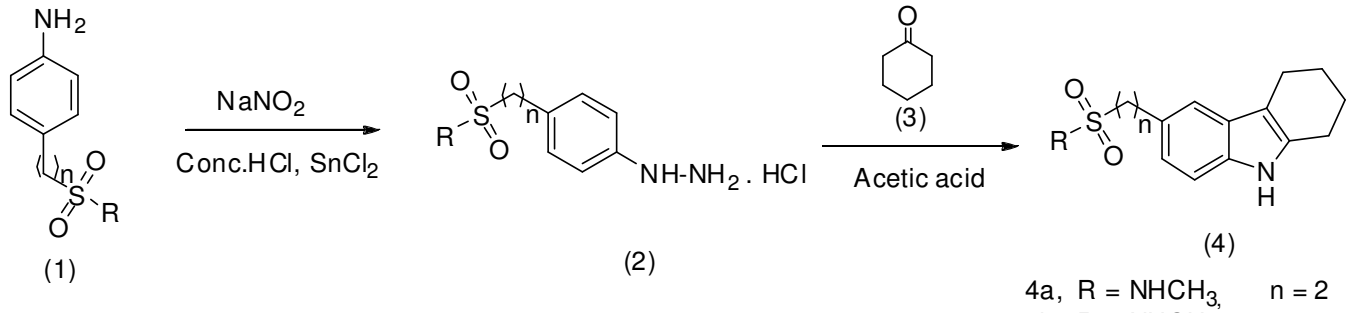
General procedure for the synthesis of 4a-c: A mixture of **2a-c** (3.16 g, 0.011 M), cyclohexanone (1.16 g, 0.011 M), sodium acetate (2.07 g, 0.015 M) and acetic acid (25 mL) was refluxed with stirring for 5 h. The solvent was distilled off under reduced pressure. The residue was partitioned between water and ethyl acetate. The organic layer was dried, concentrated and crystallized from methanol (10 mL). The crude compound was recrystallized from a suitable solvent to obtain pure **4a-c (Scheme-I)**.

Compound 4a: (R = -NHCH$_3$, n = 2), yield: 65 %, m.p.: 154-157 ºC; IR (KBr, ν_{max}, cm^{-1}) 3372,1300, 1144; ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 4H, carbazole -CH_2CH_2), 2.6 (d, 3H, -$NHCH_3$), 2.70 (m, 2H, -CH_2), 2.75 (m, 2H, -CH_2) 3.2 (m, 2H, $ArCH_2$), 3.4 (m, 2H,-CH_2SO_2), 3.8 (q, 1H, -$NHCH_3$, D_2O exchangeable), 7.0-7.4 (m, 3H, Ar-H), 7.8 (bs, 1H, indole NH, D_2O exchangeable), M+1: 293.2. Anal. calcd. for ($C_{15}H_{20}N_2O_2S$) requires: C, 61.62; H, 6.89; N, 9.58: found: C, 61.52; H, 6.81; N, 9.53.

Compound 4b: (R = -NHCH$_3$, n = 1), yield: 59 %, m.p.: 213-215 ºC; IR (KBr, ν_{max}, cm^{-1}) 3362,1290, 1120; ^{1}H NMR ($CDCl_3$-d_6/TMS) δ 1.9 (m, 4H, -CH_2CH_2), 2.6 (d, 3H, -$NHCH_3$), 2.70 (m, 2H, -CH_2), 2.75 (m, 2H, -CH_2) 3.8 (m, 1H, -$NHCH_3$, D_2O exchangeable), 4.3 (s, 2H, -$ArCH_2$), 7.0-7.4 (m, 3H, Ar-H), 7.8 (bs, 1H, indole NH, D_2O exchangeable), M+1: 278.3. Anal. calcd. for ($C_{14}H_{18}N_2O_2S$) requires: C, 60.41; H, 6.52; N, 10.06: found: C, 60.45; H, 6.50; N, 10.16.

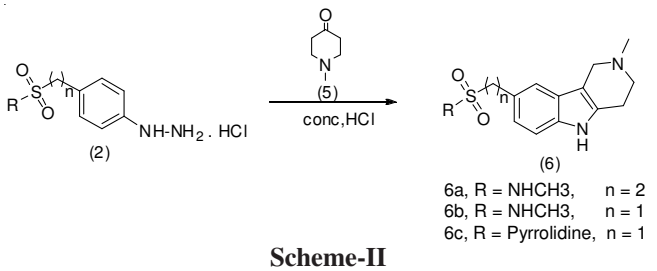
Compound 4c: (R = pyrrolidine, n = 1), yield: 64 %, m.p.: -250 ºC; IR (KBr, ν_{max}, cm^{-1}) 1300, 1144; ^{1}H NMR (DMSO-d_6/TMS) δ 1.80-1.90 (m, 8H, 4 × CH_2), 2.70 (m, 2H, -CH_2), 2.75 (m, 2H, -CH_2), 3.2 (m, 4H, pyrrolidine), 4.3 (s, 2H, -$ArCH_2$), 7.0-7.4 (m, 3H, Ar-H), 7.8 (bs, 1H, indole NH, D_2O exchangeable), M+1: 318.43. Anal. calcd. for ($C_{17}H_{22}N_2O_2S$) requires: C, 64.12; H, 6.96; N, 8.80: found: C, 64.02; H, 6.91; N, 8.80.

General procedure for the synthesis of 6a-c: The compounds **2a-c** (3.16 g, 0.011 M), was dissolved in water (47.4 mL)



Scheme-I

and *N*-methyl-4-pipridone (1.25 g, 0.011 M) was added over a period of 5 min. After addition slowly heated to 50-55 ºC and conc. HCl (7 mL) was added over 0.5 h. Reaction mass stirred at overnight at 50-55 ºC, then cooled to 25-30 ºC adjusted the pH to 12 with sodium hydroxide solution. The slurry was allowed to stir for 0.5 h and then cooled to 10-15 ºC, filtered and washed with water. The crude compound was recrystallized from a suitable solvent to get pure compound **6a-c (Scheme-II)**.



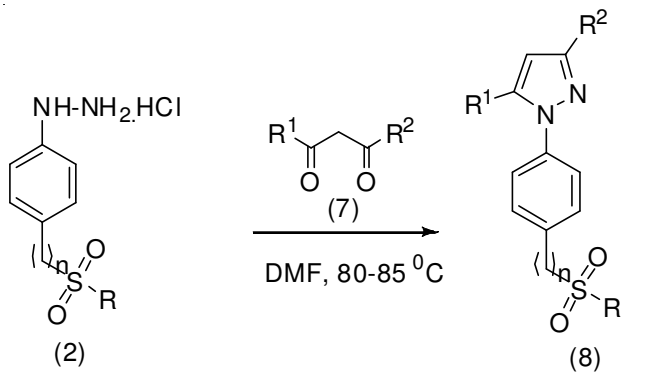
Scheme-II

Compound 6a: (R = -NHCH$_3$, n = 2), yield: 73 %, m.p.: 158-160 ºC; IR (KBr, ν_{max}, cm^{-1}) 3362,1280, 1120; ^{1}H NMR (DMSO-d_6/TMS): δ 2.4 (s, 3H, -NCH$_3$), 2.6 (d, 3H, -NHCH$_3$), 2.6-2.9 (m, 4H, 2 × -CH$_2$) 3.0 (m, 2H, - Ar CH$_2$-), 3.2 (m, 2H, -CH$_2$SO$_2$), 3.40 (s, 2H, -CH$_2$), 6.8-7.3 (m, 4H, Ar-H), 10.6 (br, s, -NH, D$_2$O exchangeable); M+1: 318.43. Anal. calcd. for (C$_{17}$H$_{22}$N$_2$O$_2$S) requires: C, 64.12; H, 6.96; N, 8.80: found: C, 64.02; H, 6.91; N, 8.80.

Compound 6b: (R = -NHCH$_3$, n = 1), yield: 49 %, m.p.: 142-145 ºC; IR (KBr, ν_{max}, cm^{-1}) 3372,1275, 1118; ^{1}H NMR (DMSO-d_6/TMS): δ 2.4 (s, 3H, -NCH$_3$), 2.6 (d, 3H, -NHCH$_3$), 2.6-2.9 (m, 4H, 2 × -CH$_2$) 3.40 (s, 2H, -CH$_2$), 4.3 (m, 2H, -CH$_2$Ar), 6.8-7.3 (m, 4H, Ar-H), 10.6 (br, s, -NH, D$_2$O exchangeable); M+1: 318.43. Anal. calcd for (C$_{17}$H$_{22}$N$_2$O$_2$S) requires: C, 64.12; H, 6.96; N, 8.80: found: C, 64.02; H, 6.91; N, 8.80.

Compound 6c: (R = pyrrolidine, n = 1), yield: 54 %, m.p.: 170-172 ºC; IR (KBr, ν_{max}, cm^{-1}) 1280, 1120; ^{1}H NMR (DMSO-d_6/TMS) δ 1.8-1.85 (m, 4H, pyrrolidine), 2.4 (s, 3H, -NCH$_3$), 2.6-2.9 (m, 4H, 2 × -CH$_2$) 3.2 (m, 4H, pyrrolidine) 3.40 (s, 2H, -CH$_2$), 4.3 (m, 2H, -CH$_2$Ar), 6.8-7.3 (m, 4H, Ar-H), 10.6 (br, s, -NH, D$_2$O exchangeable); M+1: 334.43. Anal. calcd. for (C$_{17}$H$_{23}$N$_3$O$_2$S) requires: C, 61.23; H, 6.95; N, 12.60: found: C, 61.13; H, 6.90; N, 12.58.

General procedure for the synthesis of 8a-i: The compounds **2a-c** (0.01 M) was added to a stirred solution of the 1-(thiophen-2-yl) butane-1,3-dione (**7**) (0.01 M) in *N,N*-dimethylformamide (20 mL). The mixture was heated to 80-85 ºC and stirred for 3 h. After cooling to room temperature, the reaction mixture was quenched into water (50 mL), extracted into ethyl acetate. The organic layer was washed with water and dried over anhy. MgSO$_4$. The organic layer was filtered and concentrated under vacuum to give a light brown solid. The crude product was recrystallized from methanol to give pure **8a-i (Scheme-III)**.



Scheme-III

Compound 8a: (R = -NHCH$_3$ n = 2, R^1 = thiophene, R^2 = CH$_3$), yield: 75 %, m.p.: 191-194 ºC; IR (KBr, ν_{max}, cm^{-1}) 3347, 1280, 1120 ; ^{1}H NMR (CDCl$_3$): δ 2.35 (s, 3H, pyrazole CH$_3$), 2.75 (d, 3H, -NHCH$_3$), 3.25 (m, 2H, -CH$_2$Ar), 3.45 (m, 2H, -SO$_2$CH$_2$), 4.00 (q, 1H, -NHCH$_3$, D$_2$O exchangable), 6.35 (s, 1H, pyrazole CH), 6.90 (dd, 1H, thizole protons), 6.95 (dd, 1H, thizole protons), 7.25-7.4 (m, 4H, Ar-H), 7.35 (s, 1H, thizole protons); M+1: 362. Anal. calcd. for (C$_{17}$H$_{19}$N$_3$O$_2$S$_2$) requires: C, 56.48; H, 5.30; N, 11.62: found: C, 56.40; H, 5.20; N, 11.52.

Compound 8b: (R = -NHCH$_3$, n = 1, R^1 = thiophene, R^2 = CH$_3$) yield: 79 %, m.p.: 150-152 ºC; IR (KBr, ν_{max}, cm^{-1}) 3345, 1270, 1110; ^{1}H NMR (DMSO-d_6/TMS): δ 2.30 (s, 3H, pyrazole CH$_3$), 2.75 (d, 3H, -NHCH$_3$), 4.00 (q, 1H, -NHCH$_3$, D$_2$O exchangable), 4.40 (s, 2H, -CH$_2$Ar), 6.35 (s, 1H, pyrazole CH), 6.90 (dd, 1H, thizole protons), 6.95 (dd, 1H, thizole

protons), 7.25-7.4 (m, 4H, Ar-H), 7.35 (s, 1H, thizole protons); M+1: 348. Anal. calcd for ($C_{16}H_{17}N_3O_2S_2$) requires: C, 55.31; H, 4.93; N, 12.09: found: C, 55.21; H, 4.96; N, 12.00.

Compound 8c: (R = pyrrolidine, n = 1, R^1 = thiophene, R^2 = CH_3), yield: 64 %, m.p.: 122-125 ºC; IR (KBr, ν_{max}, cm^{-1}) 1280, 1115; ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 4H, pyrrolidine), 2.30 (s, 3H, pyrazole CH), 3.3 (m, 4H, pyrrolidine), 4.30 (s, 2H, CH_2), 6.35 (s, 1H, pyrazole CH), 6.90 (dd, 1H, thizole protons), 6.95 (dd, 1H, thizole protons), 7.25-7.4 (m, 4H, Ar-H), 7.35 (s, 1H, thizole protons); M+1: 386. Anal. calcd for ($C_{20}H_{22}N_2O_2S_2$) requires: C, 62.15; H, 5.74; N, 7.25: found: C, 62.10; H, 5.64; N, 7.20.

Compound 8d: (R = -$NHCH_3$, n = 2, R^1 = phenyl, R^2 = CF_3), yield: 70 %, m.p: 174-176 ºC; IR (KBr, ν_{max}, cm^{-1}) 3343, 1265, 1130; ^{1}H NMR ($CDCl_3$): δ 2.80 (s, 3H, -$NHCH_3$), 3.20 (m, 2H, -CH_2Ar), 3.45 (m, 2H, -SO_2CH_2), 4.10 (q, 1H, -$NHCH_3$, D_2O exchangable), 6.70 (s, 1H, pyrazole CH), 7.20-7.60 (m, 9H, Ar-H); M+1: 410. Anal. calcd for ($C_{19}H_{18}F_3N_3O_2S$) requires: C, 55.74; H, 4.43; N, 10.26: found: C, 55.64; H, 4.40; N, 10.16.

Compound 8e: (R = $NHCH_3$, n = 1, R^1 = phenyl, R^2 = CF_3), yield: 64 %, m.p.: 181-183 ºC; IR (KBr, ν_{max}, cm^{-1}) 3347, 1240, 1135; ^{1}H NMR ($CDCl_3$): δ 2.75 (d, 3H, -$NHCH_3$), 4.00 (q, 1H, -$NHCH_3$, D_2O exchangeable), 4.40 (s, 2H, -CH_2Ar), 6.70 (s, 1H, pyrazole CH), 7.20-7.60 (m, 9H, Ar-H); M+1: 396. Anal. calcd. for ($C_{18}H_{16}F_3N_3O_2S$) requires: C, 54.68; H, 4.08; 10.63: found: C, 54.63; H, 4.04; 10.73.

Compound 8f: (R = pyrrolidine, n = 1, R^1 = phenyl, R^2 = CF_3), yield: 73 %, m.p.: 162-165 ºC; IR (KBr, ν_{max}, cm^{-1}) 1280, 1120; ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 4H, pyrrolidine), 3.3 (m, 4H, pyrrolidine), 4.2 (s, 2H, -CH_2), 6.70 (s, 1H, pyrazole CH), 7.20-7.60 (m, 9H, Ar-H); M+1: 435. Anal. calcd for ($C_{22}H_{21}F_3N_2O_2S$) requires: C, 60.82; H, 4.87; N, 6.45: found: C, 60.72; H, 4.85; N, 6.35.

Compound 8g: (R = $NHCH_3$, n = 2, R^1 = 4-methylphenyl, R^2 = CF_3), yield: 90 %, m.p.: 160-165 ºC; IR (KBr, ν_{max}, cm^{-1}) 3337, 1270, 1117; ^{1}H NMR (DMSO-d_6/TMS): δ 2.30 (s, 3H, -CH_3), 2.60 (s, 3H, -$NHCH_3$), 3.00 (m, 2H, -CH_2Ar), 3.30 (m, 2H, -SO_2CH_2), 6.90 (s, 1H, pyrazole CH), 7.00 (q, 1H, -$NHCH_3$, D_2O exchangable), 7.00 7.20-7.60 (m, 8H, Ar-H); M+1: 424. Anal. calcd. for ($C_{20}H_{20}F_3N_3O_2S$) requires: C, 56.73; H, 4.76; N, 9.92: found: C, 56.63; H, 4.72; N, 9.82.

Compound 8h: (R = $NHCH_3$, n = 1, R^1 = 4-methylphenyl, R^2 = CF_3), yield: 79 %, m.p.: 139-141 ºC; IR (KBr, ν_{max}, cm^{-1}) 3347, 1280, 1120; ^{1}H NMR (DMSO-d_6/TMS): δ 2.30 (s, 3H, -CH_3), 2.75 (d, 3H, -$NHCH_3$), 4.40 (s, 2H, -CH_2Ar), 6.70 (s, 1H, pyrazole CH), 4.00 (q, 1H, -$NHCH_3$, D_2O exchangeable), 7.20-7.60 (m, 9H, Ar-H); M+1: 410. Anal. calcd for ($C_{19}H_{18}F_3N_3O_2S$) requires: C, 55.74; H, 4.43; N, 10.26: found: C, 55.64; H, 4.33; N, 10.29.

Compound 8i: (R = pyrrolidine, n = 1, R^1 = 4-methylphenyl, R^2 = CF_3), yield: 94 %, m.p.: 147-149 ºC; IR (KBr, ν_{max}, cm^{-1}) 1260, 1130; ^{1}H NMR (DMSO-d_6/TMS): δ 1.92 (m, 4H, pyrrolidine), 2.30 (s, 3H, CH_3), 3.3 (m, 4H, pyrrolidine), 4.2 (s, 2H, -CH_2), 6.70 (s, 1H, pyrazole CH), 7.20-7.60 (m, 8H, Ar-H); M+1: 449. Anal. calcd for ($C_{23}H_{23}F_3N_2O_2S$) requires: C, 61.59; H, 5.17; N, 6.25: found: C, 61.49; H, 5.10; N, 6.20.

RESULTS AND DISCUSSION

The required starting materials, *viz.*, substituted 4-aminophenylmethane sulfonamides, were synthesized from 4-nitrobenzylbromide/chloride, as per the reported procedure[21]. Methyl (or) trifluoromethyl substituted aryl β-diketones were prepared form the corresponding ketones and ethyl acetoacetate (or) trifluoroethyl acetate in the presence of sodium methoxide in toluene as per the reported procedure[22]. Diazotization of *N*-methyl-4-aminophenylethanesulfonamide (**1a**) followed by reduction with stannous chloride gave 1-(4-hydrazinylphenyl)-*N*-methylethanesulfonamide hydrochloride (**2a**) in 80 % yield. This on reaction with cyclohexanone (**3**) gave a new compound *N*-methyl-2-(2,3,4,9-tetrahydro-1*H*-carbazol-6-yl)methanesulfonamide (**4a**). Its IR (KBr) spectrum showed characteristic peak at 3372 cm^{-1}, which can be attributed to -NH group. Peaks at 1300 and 1144 cm^{-1} indicate SO_2 group. Its ^{1}H NMR spectrum showed multiplets between δ 1.92-2.75, which can be assigned to eight aliphatic protons. The signals at δ 2.7 and δ 3.7 confirm the presence of -$NHCH_3$. Two multiplets at δ 3.2 and δ 3.4 corresponds to the (-Ar-CH_2-CH_2-SO_2-). The peaks between δ 7.0-7.4 confirm the three aromatic protons. Board singlet at δ 7.8 can be assigned to -NH of carbazole ring. The mass spectrum of **4a** showed the molecular ion at *m/z* 293 further supports the assigned structure.

Similarly, condensation of **2a** with *N*-methyl-4-piperidone (**5**), followed by cyclization in conc. HCl gave the corresponding *N*-methyl-2-(2-methyl-2,3,4,5- tetrahydro-1*H*-pyrido[4,3-b]indol-8-yl)ethanesulfonamide (**6a**). Its IR (KBr) spectrum showed characteristic peak at 3362 cm^{-1}, which can be attributed to -NH group. Peaks at 1300 and 1144 cm^{-1} indicate SO_2 group. Its ^{1}H NMR spectrum showed signal at δ 2.4 (3H) and 2.6 (3H), which can be attributed to methyl protons of -$NHCH_3$ and -NCH_3 respectively. Two multiplets between δ 2.70-2.78 can be assigned to -CH_2-CH_2NCH_3. Two multiplites between δ 2.9-3.2 (4H) due to (-Ar-CH_2-CH_2-SO_2-). The singlet at δ 3.4 (2H) can be assigned to -CH_2NCH_3. The aromatic protons and -$NHCH_3$ proton appeared between δ 6.8-7.1 as a multiplet. A singlet at δ 10.6 can be attributed to -NH proton of carbazole. The mass spectrum of **6a** showed a molecular ion at *m/z* 308.1.

Condensation of **2a** with 1-(thiophen-2-yl)butane-1,3-dione (**7**) in *N,N*-dimethylformamide at 80-85 ºC gave a new compound 3-methyl-1-(4-((pyrrolidin-1-ylsulfonyl)methyl) phenyl)-5-(thiophen-2-yl)-1H-pyrazole (**8a**) as the major product regioselectively, which was purified by recrystization from methanol gave pure compound. Its IR (KBr) spectrum showed characteristic peak at 3372 cm^{-1} (-NH) and at 1300 and 1144 cm^{-1} (SO_2) group. Its ^{1}H NMR spectrum showed three proton singlet at δ 2.35 due to the methyl group of pyrazole and doublet at δ 2.75 is due to -$NHCH_3$. Two multiplets at δ 3.25-3.45 can be assigned to (-Ph-CH_2-CH_2-SO_2-). A quartet appeared δ 4.0 is due to -$NHCH_3$. A singlet at δ 6.35 can be assigned to pyrazole-CH. The multiplet between δ 6.9-7.3 with seven proton integration can be assigned to the four protons of phenyl group and three protons of thiazole group. The mass spectrum of **8a** showed the molecular ion at *m/z* 362.1.

Conclusion

In conclusion, we have prepared some new substituted carbazoles and pyrazole derivatives containing benzene methane/ethane sulfonamide. Further studies are desirable to evaluate their biological activities.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Satyanarayana Jangani, Dr. Venkateswara Kumar Taduri and Dr. Ravi Kumar Dissymmetrix Pvt. Ltd., Uppal, Hyderabad, India for their fruitful encouragement.

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