International Journal of Organic Chemistry, **2011, 1, 78-86**
doi:10.4236/ijoc.2011.13013 Published Online September 2011 (http://www.SciRP.org/journal/ijoc)

Synthesis and Antimicrobial Activity of a New Class of Sulfone Linked Bisheterocycles

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Received June 1, 2011; *revised July* 20, 2011; *accepted August* 1, 2011

Abstract

A new and novel class of bis(heterocycles) *viz*., bis pyrroles, pyrrolyl pyrazoles and pyrrolyl isoxazoles are prepared from 1-aroyl-2-styrylsulfonylethenes by 1,3-dipolar cycloaddition of tosylmethyl isocyanide, diazomethane, nitrile imines and nitrile oxides. The lead compounds are screened for antimicrobial activity.

Keywords: 1-Aroyl-2-Styrylsulfonylethene, 1,3-Dipolar Cycloaddition, Chloramine-T, Antimicrobial Activity

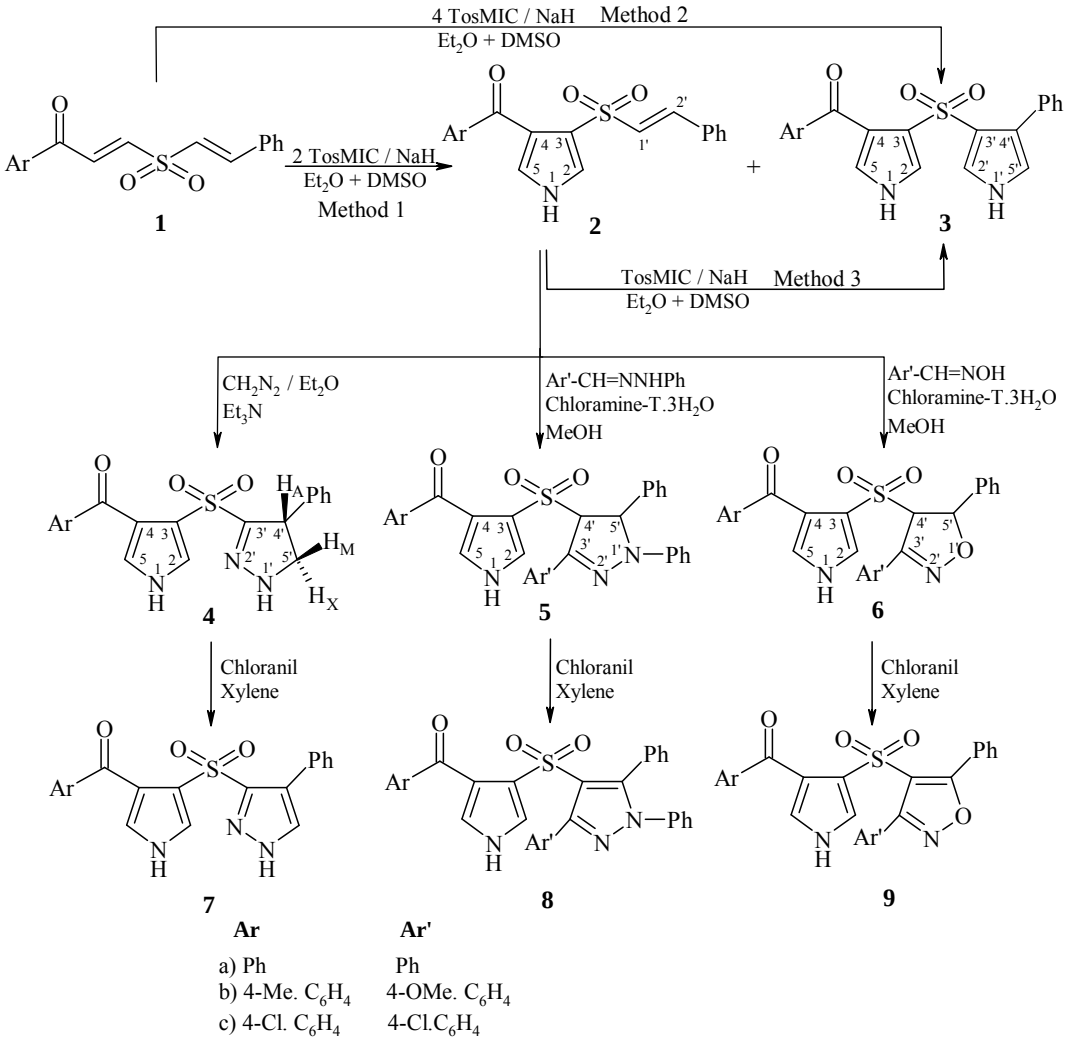
1. Introduction

In the last few decades the chemistry of five-membered heterocycles particularly pyrroles, pyrazolines and isoxazolines has received considerable attention owing to their synthetic and effective biological importance. Increasing evidence suggests that pyrazoline derivatives possess a broad spectrum of biological activities such as antidepressant, anticonvulsant, psychoanalytic, antihypotensive and monamine oxidase inhibitory activities [1, 2]. In fact, Celecoxib, a pyrazole derivative and Valdecoxib an isoxazole derivative are extensively used as anti-inflammatory drugs [3]. Besides, pyrrole carboxylates exhibit antibiotic, antiviral and oncolytic properties [4-8]. Hence, it is thought that a worthwhile programme would be to prepare molecules having both pyrrole and pyrazole/isoxazole units. Literature evidenced the synthesis of 3,4-disubstituted pyrroles by cyclocondensation of Michael acceptors with tosylmethyl isocyanide (TosMIC) [9]. Pyrroles have also been prepared by Paal-Knorr condensation of alkyl and aryl amines with 1,4-diketones [10-13]. Similarly, among different methods for the synthesis of pyrazolines and isoxazolines, 1,3-dipolar cycloaddition of an ylide onto an alkene in a 3 + 2 manner is a facile one [14,15]. Indeed, diazomethane, nitrile imines and nitrile oxides have been used extensively as reactive intermediates. The nitrile imines and nitrile oxides can be generated by dehydrogenation of araldehyde phenylhydrazones and araldoximes with lead tetraacetate [16], mercuric acetate [17], 1-chlorobenzotriazole [18], chloramine-T [19-22] etc. The present communication deals with the synthesis of sulfone linked bis heterocycles having a pyrrole in combination with a pyrazole or an isoxazole unit.

2. Results and Discussion

The synthetic scheme is based on the reactivity of 1-aroyl-2-styrylsulfonylethene (**1**) towards 1,3-dipolar reagents *viz*., TosMIC, diazomethane, nitrile imines, nitrile oxides. When compound (**1**) is treated with TosMIC in the presence of sodium hydride in a mixture of ether and DMSO, the reaction took place regioselectively resulting in a mixture of compounds in 3:1 ratio. They are identified as 4-aroyl-3-(phenylethenesulfonyl)-1*H*-pyrrole (**2**) and 4-aroyl-3-(4'-phenyl-1'*H*-pyrrol-3'-ylsulfonyl)-1*H*-pyrrole (**3**) in major and minor amounts, respectively (**Scheme 1**, **Table 1**). However, repetition of this reaction with excess TosMIC resulted in **3** only. The latter compound is also obtained by treating **2** with one equivalent of TosMIC. The ^{1}H NMR spectrum of **2a** showed two singlets at δ 7.01 and 8.02 ppm for C_2-H, and C_5-H of pyrrole ring protons. Two doublets are observed at 6.79 and 7.48 ppm corresponding to olefin protons in addition to the signals of the aromatic protons. The coupling constants value (J = 17.8 Hz) indicates that they are in *trans* geometry. Compound **3a** exhibited three singlets at δ 6.89 (C_2-H & $C_{2'}$-H), 6.96 ($C_{5'}$-H) and 8.04 (C_5-H) ppm apart from signals due to aromatic protons (**Table 2**).

The olefin moiety in **2** is used to develop different het-



Scheme 1. Synthesis of bis heterocycles.

erocyclic rings such as pyrazoles and isoxazoles. Treatment of **2** with diazomethane at –20˚C to –15˚C for 48 h gave a solid which is identified as 4-aroyl-3-(4'-phenyl-4',5'-dihydro-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**4**) by spectral analysis. The ^{1}H NMR spectrum of 4a showed an AMX splitting pattern for the pyrazoline ring protons exhibiting three double doublets at δ 4.54 (H_A), 3.99 (H_M) and 3.64 (H_X) ppm, apart from the signals of aromatic and pyrrole ring protons. The observed coupling constant values J_{AM} = 11.6, J_{AX} = 5.1 and J_{MX} = 10.3 Hz indicates that H_A and H_M are *cis*, H_A and H_X are *trans* and H_M and H_X are *geminal* (**Table 2**). Similarly, 1,3-dipolar cycloaddition reaction of nitrile imines and nitrile oxides generated from araldehyde phenylhydrazones and araldoximes to **2** resulted in 4-aroyl-3-(1',5'-diphenyl-3'-aryl-4',5'-dihydro-1'*H*-pyrazol-4'-ylsulfonyl)-1*H*-pyrrole (**5**) and 4-aroyl-3-(3'-aryl-5'-phenyl-4',5'-dihydroisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (**6**), respectively (**Scheme 1**, **Table 1**). The ^{1}H-NMR spectra of **5a** and **6a** displayed two doublets at δ 5.19, 5.22 and 5.58, 5.66 ppm, which are assigned to $C_{4'}$-H and $C_{5'}$-H, the two methine protons of the pyrazoline and isoxazo- line rings. The *J* values (*J* = 6.3 & 6.4 Hz) shows that they are in *trans* geometry.

The olefin moiety in **2** is used to develop different heterocyclic rings such as pyrazoles and isoxazoles. Treatment of **2** with diazomethane at –20˚C to –15˚C for 48 h gave a solid which is identified as 4-aroyl-3-(4'-phenyl-4',5'-dihydro-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**4**) by spectral analysis. The ^{1}H NMR spectrum of **4a** showed an AMX splitting pattern for the pyrazoline ring protons exhibiting three double doublets at δ 4.54 (H_A), 3.99 (H_M) and 3.64 (H_X) ppm, apart from the signals of aromatic and pyrrole ring protons. The observed coupling constant values J_{AM} = 11.6, J_{AX} = 5.1

Table 1. Physical characterization data of compounds 2-9.

Compd	m.p. (°C)	Yield (%)	Mol. Formula (Mol. wt.)	Found % (Calcd)		
				C	H	N
2a	178 - 80	56	$C_{19}H_{15}NO_3S$ (337.39)	67.71 (67.64)	5.01 (4.48)	4.22 (4.15)
2b	169 - 71	54	$C_{20}H_{17}NO_3S$ (351.42)	68.50 (68.36)	4.82 (4.88)	4.04 (3.99)
2c	211 - 13	60	$C_{19}H_{14}ClNO_3S$ (371.84)	61.32 (61.37)	3.83 (3.79)	3.81 (3.77)
3a	185 - 87	16, 70[a], 72[b]	$C_{21}H_{16}N_2O_3S$ (376.43)	67.12 (67.00)	4.27 (4.28)	7.52 (7.44)
3b	192 - 94	10, 64[a], 71[b]	$C_{22}H_{18}N_2O_3S$ (390.45)	67.75 (67.67)	4.69 (4.65)	7.14 (7.17)
3c	220 - 22	12, 68[a], 76[b]	$C_{21}H_{15}ClN_2O_3S$ (410.87)	61.46 (61.39)	3.70 (3.68)	6.85 (6.82)
4a	196 - 98	67	$C_{20}H_{17}N_3O_3S$ (379.43)	63.26 (63.31)	4.57 (4.52)	11.11 (11.07)
4b	207 - 09	70	$C_{21}H_{19}N_3O_3S$ (393.46)	64.18 (64.10)	4.84 (4.87)	10.72 (10.68)
4c	235 - 37	73	$C_{20}H_{16}ClN_3O_3S$ (413.88)	58.00 (58.04)	3.94 (3.90)	10.22 (10.15)
5a	225 - 27	72	$C_{32}H_{25}N_3O_3S$ (531.62)	72.37 (72.30)	4.80 (4.74)	7.96 (7.90)
5b	212 - 14	69	$C_{34}H_{29}N_3O_4S$ (575.68)	70.88 (70.94)	5.05 (5.08)	7.36 (7.30)
5c	243 - 45	75	$C_{32}H_{23}Cl_2N_3O_3S$ (600.51)	64.06 (64.00)	3.82 (3.86)	7.05 (7.00)
6a	202 - 04	76	$C_{26}H_{20}N_2O_4S$ (456.51)	68.50 (68.41)	4.44 (4.42)	6.10 (6.14)
6b	215 - 17	74	$C_{28}H_{24}N_2O_5S$ (500.57)	67.14 (67.18)	4.82 (4.83)	5.63 (5.60)
6c	231 - 33	78	$C_{26}H_{18}Cl_2N_2O_4S$ (525.40)	59.51 (59.44)	3.50 (3.45)	5.38 (5.33)
7a	204 - 06	65	$C_{20}H_{15}N_3O_3S$ (377.42)	63.73 (63.65)	4.04 (4.01)	11.26 (11.13)
7b	214 - 16	62	$C_{21}H_{17}N_3O_3S$ (391.44)	64.49 (64.43)	4.40 (4.38)	10.80 (10.73)
7c	247 - 49	67	$C_{20}H_{14}ClN_3O_3S$ (411.86)	58.38 (58.32)	3.48 (3.43)	10.30 (10.20)
8a	237 - 39	64	$C_{32}H_{23}N_3O_3S$ (529.61)	72.70 (72.57)	4.37 (4.38)	8.00 (7.93)
8b	242 - 44	70	$C_{34}H_{27}N_3O_4S$ (573.66)	71.29 (71.19)	4.79 (4.74)	7.28 (7.32)
8c	269 - 71	68	$C_{32}H_{21}Cl_2N_3O_3S$ (598.50)	64.31 (64.22)	3.51 (3.54)	7.08 (7.02)
9a	211 - 13	66	$C_{26}H_{18}N_2O_4S$ (454.50)	68.78 (68.71)	4.03 (3.99)	6.13 (6.16)
9b	227 - 29	63	$C_{28}H_{22}N_2O_5S$ (498.55)	67.48 (67.46)	4.48 (4.45)	5.57 (5.62)
9c	246 - 48	72	$C_{26}H_{16}Cl_2N_2O_4S$ (523.39)	59.75 (59.66)	3.08 (3.06)	5.41 (5.35)

[a]Yield in Method-2; [b]Yield in Method-3

Table 2. IR, ^{1}H and ^{13}C NMR spectral characterization data of compounds 2-9.

Compd	IR (KBr) cm^{-1}	^{1}H NMR (δ, ppm) (*J* in Hz)	^{13}C NMR (δ, ppm)
2a	3326 (NH), 1660 (C=O), 1641 (C=C), 1334, 1131 (SO_2)	6.79 (d, 1H, $C_{1'}$-H, *J* = 17.8 Hz), 7.01 (s, 1H, C_2-H), 7.48 (d, 1H, $C_{2'}$-H, *J* = 17.8 Hz), 7.14 - 7.85 (m, 10H, Ar-H), 8.02 (s, 1H, C_5-H), 10.79 (bs, 1H, NH)	108.6 (C-3), 117.3 (C-4), 120.0 (C-1'), 121.4 (C-2), 136.9 (C-5), 137.7 (C-2'), 189.4 (C=O), 128.4, 129.6, 130.9, 131.5, 132.9, 133.7, 134.4 (aromatic carbons)
2b	3330 (NH), 1667 (C=O), 1634 (C=C), 1328, 1139 (SO_2)	2.28 (s, 3H, Ar-CH_3), 6.73 (d, 1H, $C_{1'}$-H, *J* = 17.5 Hz), 7.05 (s, 1H, C_2-H), 7.42 (d, 1H, $C_{2'}$-H, *J* = 17.5 Hz), 7.17 - 7.82 (m, 9H, Ar-H), 8.05 (s, 1H, C_5-H), 10.72 (bs, 1H, NH)	21.7 (Ar-CH_3), 109.1 (C-3), 117.9 (C-4), 120.8 (C-1'), 121.6 (C-2), 136.4 (C-5), 137.1 (C-2'), 188.7 (C=O), 129.5, 130.6, 131.9, 132.5, 133.4, 134.0, 134.8 (aromatic carbons)
2c	3335 (NH), 1664 (C=O), 1635 (C=C), 1337, 1130 (SO_2)	6.77 (d, 1H, $C_{1'}$-H, *J* = 17.7 Hz), 7.07 (s, 1H, C_2-H), 7.46 (d, 1H, $C_{2'}$-H, *J* = 17.7 Hz), 7.21 - 7.89 (m, 9H, Ar-H), 8.01 (s, 1H, C_5-H), 10.81 (bs, 1H, NH)	108.8 (C-3), 118.3 (C-4), 121.2 (C-1'), 121.3 (C-2), 136.2 (C-5), 137.4 (C-2'), 189.6 (C=O), 128.2, 129.6, 130.3, 131.7, 133.8, 134.9, 135.6 (aromatic carbons)
3a	3329 (NH), 1662 (C=O), 1331, 1129 (SO_2)	6.89 (s, 2H, C_2-H and $C_{2'}$-H), 6.96 (s, 1H, $C_{5'}$-H), 7.25 - 7.78 (m, 10H, Ar-H), 8.04 (s, 1H, C_5-H), 10.42 (bs, 2H, NH)	105.3 (C-4'), 109.6 (C-3 and C-3'), 115.3 (C-4), 118.5 (C-2 and C-2'), 119.7 (C-5'), 138.2 (C-5), 188.4 (C=O), 128.2, 129.5, 130.6, 131.3, 132.9, 133.7, 134.6, 135.2 (aromatic carbons)
3b	3324 (NH), 1668 (C=O), 1335, 1139 (SO_2)	2.25 (s, 3H, Ar-CH_3), 6.85 (s, 2H, C_2-H and $C_{2'}$-H), 6.99 (s, 1H, $C_{5'}$-H), 7.19-7.74 (m, 9H, Ar-H), 8.02 (s, 1H, C_5-H), 10.32 (bs, 2H, NH)	22.4 (Ar-CH_3), 105.7 (C-4'), 109.2 (C-3 and 3'), 116.0 (C-4), 118.9 (C-2 and 2'), 119.4 (C-5'), 137.9 (C-5), 187.0 (C=O), 129.8, 131.2, 131.7, 132.3, 132.9, 133.4, 133.9 (aromatic carbons)
3c	3330 (NH), 1666 (C=O), 1329, 1126 (SO_2)	7.13 (s, 2H, C_2-H and $C_{2'}$-H), 7.35 (s, 1H, $C_{5'}$-H), 7.26 - 7.99 (m, 9H, Ar-H), 8.12 (s, 1H, C_5-H), 10.55 (bs, 2H, NH)	104.8 (C-4'), 108.3 (C-3 and C-3'), 115.3 (C-4), 118.5 (C-2 and C-2'), 121.8 (C-5'), 138.3 (C-5), 187.5 (C=O), 128.3, 129.1, 129.8, 130.6, 132.4, 133.0, 137.4, 138.3 (aromatic carbons)
4a	3323 (NH), 1664 (C=O), 1570 (C=N), 1325, 1138 (SO_2)	3.64 (dd, 1H, H_X), 3.99 (dd, 1H, H_M, J_{MX} = 10.3 Hz), 4.54 (dd, 1H, H_A, J_{AM} = 11.6 Hz, J_{AX} = 5.1 Hz), 6.18 (s, 1H, C_2-H), 7.22 - 7.40 (m, 10H, Ar-H), 7.80 (s, 1H, C_5-H), 8.94 (bs, 1H, NH), 10.41 (bs, 1H, NH)	48.7 (C-5'), 57.5 (C-4'), 109.8 (C-3), 116.4 (C-4), 121.8 (C-2), 138.3 (C-5), 151.8 (C-3'), 188.7 (C=O), 127.1, 128.5, 128.8, 129.4, 130.7, 132.9, 134.1, 137.3 (aromatic carbons)
4b	3342 (NH), 1662 (C=O), 1576 (C=N), 1317, 1140 (SO_2)	2.28 (s, 3H, Ar-CH_3), 3.85 (dd, 1H, H_X), 4.22 (dd, 1H, H_M, J_{MX} = 8.2 Hz), 4.54 (dd, 1H, H_A, J_{AM} = 12.0 Hz, J_{AX} = 4.3 Hz), 6.94 (s, 1H, C_2-H), 7.22 - 7.64 (m, 9H, Ar-H), 7.95 (s, 1H, C_5-H), 8.89 (bs, 1H, NH), 10.36 (bs, 1H, NH)	22.4 (Ar-CH_3), 48.1 (C-5'), 58.5 (C-4'), 108.9 (C-3), 116.6 (C-4), 121.9 (C-2), 136.3 (C-5), 152.8 (C-3'), 188.6 (C=O), 128.3, 129.2, 130.4, 131.6, 132.7, 133.8, 134.2, 135.3 (aromatic carbons)
4c	3320 (NH), 1669 (C=O), 1569 (C=N), 1321, 1131 (SO_2)	3.83 (dd, 1H, H_X), 4.27 (dd, 1H, H_M, J_{MX} = 8.0 Hz), 4.56 (dd, 1H, H_A, J_{AM} = 12.1 Hz, J_{AX} = 4.5 Hz), 6.97 (s, 1H, C_2-H), 7.29 - 7.74 (m, 9H, Ar-H), 7.93 (s, 1H, C_5-H), 8.94 (bs, 1H, NH), 10.39 (bs, 1H, NH)	48.7 (C-5'), 59.2 (C-4'), 108.1 (C-3), 116.9 (C-4), 122.6 (C-2), 136.9 (C-5), 153.2 (C-3'), 187.1 (C=O), 128.6, 129.4, 130.8, 131.7, 132.6, 133.2, 135.6, 138.1 (aromatic carbons)
5a	3332 (NH), 1682 (C=O), 1572 (C=N), 1328, 1123 (SO_2)	5.19 (d, 1H, $C_{4'}$-H, *J* = 6.3 Hz), 5.58 (d, 1H, $C_{5'}$-H, *J* = 6.3 Hz), 6.99 (s, 1H, C_2-H), 7.21 - 7.74 (m, 20H, Ar & Ar'-H), 8.01 (s, 1H, C_5-H), 10.71 (bs, 1H, NH)	61.9 (C-4'), 82.8 (C-5'), 108.9 (C-3), 117.4 (C-4), 121.9 (C-2), 136.2 (C-5), 155.2 (C-3'), 188.4 (C=O), 127.3, 128.1, 128.6, 129.2, 130.2, 131.2, 132.7, 133.4, 134.6, 136.3 (aromatic carbons)
5b	3336 (NH), 1678 (C=O), 1564 (C=N), 1335, 1133 (SO_2)	2.25 (s, 3H, Ar-CH_3), 3.72 (s, 3H, OCH_3), 5.23 (d, 1H, $C_{4'}$-H, *J* = 6.5 Hz), 5.54 (d, 1H, $C_{5'}$-H, *J* = 6.5 Hz), 6.94 (s, 1H, C_2-H), 7.29 - 7.71 (m, 18H, Ar & Ar'-H), 7.98 (s, 1H, C_5-H), 10.67 (bs, 1H, NH)	22.6 (Ar-CH_3), 55.6 (-OCH_3), 62.5 (C-4'), 84.8 (C-5'), 108.2 (C-3), 117.9 (C-4), 121.2 (C-2), 135.2 (C-5), 154.9 (C-3'), 187.7 (C=O), 126.2, 127.6, 128.7, 129.4, 130.9, 131.2, 132.7, 133.2, 134.8, 135.6 (aromatic carbons)
5c	3347 (NH), 1684 (C=O), 1573 (C=N), 1331, 1135 (SO_2)	5.27 (d, 1H, $C_{4'}$-H, *J* = 6.8 Hz), 5.64 (d, 1H, $C_{5'}$-H, *J* = 6.8 Hz), 6.98 (s, 1H, C_2-H), 7.25 - 7.88 (m, 18H, Ar & Ar'-H), 8.03 (s, 1H, C_5-H), 10.64 (bs, 1H, NH)	63.1 (C-4'), 83.2 (C-5'), 108.5 (C-3), 117.5 (C-4), 121.8 (C-2), 135.6 (C-5), 155.5 (C-3'), 188.6 (C=O), 127.2, 128.6, 129.2, 129.9, 130.5, 131.8, 132.3, 133.1, 135.2, 137.1 (aromatic carbons)

6a	3340 (NH), 1662 (C=O), 1577 (C=N), 1336, 1131 (SO_2)	5.22 (d, 1H, $C_{4'}$-H, J = 6.4 Hz), 5.66 (d, 1H, $C_{5'}$-H, J = 6.4 Hz), 6.93 (s, 1H, C_2-H), 7.19 - 7.71 (m, 15H, Ar & Ar'-H), 8.01 (s, 1H, C_5-H), 10.61 (bs, 1H, NH)	62.4 (C-4'), 83.6 (C-5'), 108.7 (C-3), 116.9 (C-4), 122.5 (C-2), 136.8 (C-5), 155.0 (C-3'), 189.5 (C=O), 128.3, 129.1, 129.9, 130.2, 130.6, 131.2, 132.7, 133.4, 134.6, 136.3 (aromatic carbons)
6b	3337 (NH), 1669 (C=O), 1581 (C=N), 1329, 1130 (SO_2)	2.23 (s, 3H, Ar-CH_3), 3.69 (s, 3H, OCH_3), 5.24 (d, 1H, $C_{4'}$-H, J = 6.5 Hz), 5.71 (d, 1H, $C_{5'}$-H, J = 6.5 Hz), 6.98 (s, 1H, C_2-H), 7.21 - 7.68 (m, 13H, Ar & Ar'-H), 7.99 (s, 1H, C_5-H), 10.52 (bs, 1H, NH)	21.7 (Ar-CH_3), 56.1 (-OCH_3), 63.1 (C-4'), 84.6 (C-5'), 108.3 (C-3), 117.6 (C-4), 122.1 (C-2), 135.3 (C-5), 155.6 (C-3'), 188.3 (C=O), 127.2, 128.3, 129.6, 130.9, 131.4, 133.4, 133.9, 134.0, 134.5 (aromatic carbons)
6c	3332 (NH), 1667 (C=O), 1570 (C=N), 1339, 1142, (SO_2)	5.27 (d, 1H, $C_{4'}$-H, J = 6.4 Hz), 5.76 (d, 1H, $C_{5'}$-H, J = 6.4 Hz), 7.02 (s, 1H, C_2-H), 7.25 - 7.78 (m, 13H, Ar & Ar'-H), 8.06 (s, 1H, C_5-H), 10.47 (bs, 1H, NH)	62.7 (C-4'), 84.0 (C-5'), 108.9 (C-3), 116.5 (C-4), 122.9 (C-2), 134.9 (C-5), 154.2 (C-3'), 189.1 (C=O), 128.7, 129.2, 130.9, 131.4, 132.7, 133.2, 134.8, 135.3, 137.2 (aromatic carbons)
7a	3339 (NH), 1656 (C=O), 1632 (C=C), 1564 (C=N), 1337, 1121 (SO_2)	6.38 (bs, 1H, NH), 6.98 (s, 1H, C_2-H), 7.26 - 7.62 (m, 11H, C_5'-H & Ar-H), 7.96 (s, 1H, C_5-H), 8.84 (bs, 1H, NH)	110.1 (C-3), 115.9 (C-4), 122.1 (C-2), 135.2 (C-5), 137.3 (C-5'), 139.8 (C-4'), 153.4 (C-3'), 188.3 (C=O), 128.1, 129.7, 130.7, 131.1, 132.4, 133.9, 134.2, 135.2 (aromatic carbons)
7b	3328 (NH), 1668 (C=O), 1644 (C=C), 1574 (C=N), 1326, 1138 (SO_2)	2.31 (s, 3H, Ar-CH_3), 6.44 (bs, 1H, NH), 7.01 (s, 1H, C_2-H), 7.28 - 7.71 (m, 10H, C_5'-H & Ar-H), 7.99 (s, 1H, C_5-H), 8.72 (bs, 1H, NH)	22.7 (Ar-CH_3), 109.5 (C-3), 115.1 (C-4), 122.9 (C-2), 134.8 (C-5), 136.6 (C-5'), 138.3 (C-4'), 154.7 (C-3'), 189.4 (C=O), 128.6, 129.3, 130.1, 131.8, 132.7, 133.2, 134.0, 134.9 (aromatic carbons)
7c	3336 (NH), 1666 (C=O), 1640 (C=C), 1567 (C=N), 1330, 1122 (SO_2)	6.39 (bs, 1H, NH), 6.97 (s, 1H, C_2-H), 7.21 - 7.78 (m, 10H, C_5'-H & Ar-H), 8.03 (s, 1H, C_5-H), 8.79 (bs, 1H, NH)	110.4 (C-3), 114.7 (C-4), 122.2 (C-2), 135.0 (C-5), 135.1 (C-5'), 138.2 (C-4'), 155.2 (C-3'), 188.9 (C=O), 127.4, 128.7, 130.6, 131.2, 132.3, 133.5, 134.6, 135.0, 135.6 (aromatic carbons)
8a	3331 (NH), 1658 (C=O), 1637 (C=C), 1578 (C=N), 1335, 1126 (SO_2)	7.04 (s, 1H, C_2-H), 7.19 - 7.65 (m, 20H, Ar & Ar'-H), 7.97 (s, 1H, C_5-H), 10.46 (bs, 1H, NH)	109.9 (C-3), 116.4 (C-4), 121.9 (C-2), 136.9 (C-5), 146.5 (C-3'), 147.8 (C-4'), 153.2 (C-5'), 187.8 (C=O), 127.0, 127.9, 128.7, 129.2, 129.9, 130.9, 131.8, 132.4, 133.9, 134.2, 135.3 (aromatic carbons)
8b	3338 (NH), 1669 (C=O), 1641 (C=C), 1569 (C=N), 1339, 1130 (SO_2)	2.29 (s, 3H, Ar-CH_3), 3.71 (s, 3H, OCH_3), 6.98 (s, 1H, C_2-H), 7.22 - 7.71 (m, 18H, Ar & Ar'-H), 7.99 (s, 1H, C_5-H), 10.38 (bs, 1H, NH)	22.4 (Ar-CH_3), 56.6 (-OCH_3), 109.2 (C-3), 116.9 (C-4), 122.6 (C-2), 136.2 (C-5), 146.9 (C-3'), 148.2 (C-4'), 152.9 (C-5'), 188.5 (C=O), 128.2, 129.1, 129.7, 130.2, 131.5, 132.9, 133.5, 134.0, 134.7 (aromatic carbons)
8c	3335 (NH), 1671 (C=O), 1645 (C=C), 1565 (C=N), 1333, 1128 (SO_2)	7.01 (s, 1H, C_2-H), 7.27 - 7.83 (m, 18H, Ar & Ar'-H), 8.01 (s, 1H, C_5-H), 10.42 (bs, 1H, NH)	109.5 (C-3), 116.1 (C-4), 121.8 (C-2), 136.4 (C-5), 146.1 (C-3'), 148.9 (C-4'), 152.2 (C-5'), 189.4 (C=O), 128.7, 129.4, 129.9, 130.5, 131.9, 132.2, 133.3, 134.6, 135.9 (aromatic carbons)
9a	3328 (NH), 1682 (C=O), 1656 (C=C), 1571 (C=N), 1327, 1138 (SO_2)	6.96 (s, 1H, C_2-H), 7.09 - 7.68 (m, 15H, Ar & Ar'-H), 8.01 (s, 1H, C_5-H), 10.48 (bs, 1H, NH)	108.4 (C-3), 116.1 (C-4), 119.3 (C-2), 138.4 (C-5), 147.1 (C-4'), 148.3 (C-3'), 151.8 (C-5'), 187.7 (C=O), 130.0, 130.3, 130.4, 130.6, 130.8, 131.0, 132.7, 134.1 (aromatic carbons)
9b	3339 (NH), 1678 (C=O), 1651 (C=C), 1579 (C=N), 1321, 1135 (SO_2)	2.26 (s, 3H, Ar-CH_3), 3.67 (s, 3H, -OCH_3), 6.92 (s, 1H, C_2-H), 7.14 - 7.76 (m, 13H, Ar & Ar'-H), 8.03 (s, 1H, C_5-H), 10.31 (bs, 1H, NH)	22.7 (Ar-CH_3), 57.8 (-OCH_3), 109.1 (C-3), 117.2 (C-4), 122.9 (C-2), 135.7 (C-5), 146.9 (C-4'), 148.8 (C-3'), 152.9 (C-5'), 189.9 (C=O), 127.6, 128.2, 128.7, 130.7, 131.3, 131.9, 132.8, 133.1, 134.8 (aromatic carbons)
9c	3332 (NH), 1684 (C=O), 1648 (C=C), 1583 (C=N), 1339, 1145 (SO_2)	7.03 (s, 1H, C_2-H), 7.21 - 7.82 (m, 13H, Ar & Ar'-H), 7.99 (s, 1H, C_5-H), 10.43 (bs, 1H, NH)	109.6 (C-3), 117.9 (C-4), 122.4 (C-2), 135.9 (C-5), 146.2 (C-4'), 148.3 (C-3'), 153.4 (C-5'), 189.7 (C=O), 128.6, 129.5, 130.4, 131.2, 132.6, 133.1, 133.9, 134.7, 135.9 (aromatic carbons)

and J_{MX} = 10.3 Hz indicates that H_A and H_M are *cis*, H_A and H_X are *trans* and H_M and H_X are *geminal* (**Table 2**). Similarly, 1,3-dipolar cycloaddition reaction of nitrile imines and nitrile oxides generated from araldehyde phenylhydrazones and araldoximes to **2** resulted in 4-aroyl-3-(1',5'-diphenyl-3'-aryl-4',5'-dihydro-1'*H*-pyrazol-4'-ylsulfonyl)-1*H*-pyrrole (**5**) and 4-aroyl-3-(3'-aryl-5'-phenyl-4',5'-dihydroisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (**6**), respectively (**Scheme 1**, **Table 1**). The ^{1}H-NMR spectra of **5a** and **6a** displayed two doublets at δ 5.19, 5.22 and 5.58, 5.66 ppm, which are assigned to $C_{4'}$-H and $C_{5'}$-H, the two methine protons of the pyrazoline and isoxazoline rings. The *J* values (*J* = 6.3 & 6.4 Hz) shows that they are in *trans* geometry.

The compounds **4**, **5** and **6** upon oxidation with chloranil in xylene gave the corresponding pyrazoles and isoxazoles, 4-aroyl-3-(4'-phenyl-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**7**), 4-aroyl-3-(1',5'-diphenyl-3'-aryl-1'*H*-pyrazol-4'-ylsulfonyl)-1*H*-pyrrole (**8**) and 4-aroyl-3-(3'-aryl-5'-phenylisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (9) (**Scheme 1**, **Table 1**). The disappearance of signals due to pyrazoline/isoxazoline ring protons in the ^{1}H NMR spectra of **7-9** confirms their formation. The structures of **2-9** are further established by elemental analyses, IR and ^{13}C NMR spectroscopy (**Tables 1** and **2**).

3. Antimicrobial Testing

The compounds **2**, **3**, **7-9** were tested for antimicrobial activity at two different concentrations 100 and 200 μg/mL. The antibacterial activity was screened against Staphylococcus aureus, Bacillus subtilis (Gram-positive bacteria) and Escherichia coli, Klebsiella pneumoniae (Gram-negative bacteria) on nutrient agar plates at 37˚C for 24 hr using chloramphenicol as reference drug. The compounds were also evaluated for their antifungal activity against Fusarium solani, Curvularia lunata and Aspergillus niger using ketoconazole as standard drug. Fungi cultures were grown on potato dextrose agar medium (PDA) at 25˚C for 3 days. The spore suspension was adjusted to 106 pores/mL at an mg/mL concentration by the Vincent and Vincent method [23].

The results of the compounds of preliminary antibacterial testing are shown in **Table 3**. The results revealed that the compounds **2** and **3** exhibited least activity against Gram-positive bacteria and almost no activity against Gram-negative bacteria. However, the other compounds showed higher inhibitory activity against Gram-positive bacteria than that of Gram-negative bacteria. It was reported that good DNA binding properties are a prerequisite for antibacterial activity [8]. This was evidenced by the fact that the compounds **7** showed good activity when compared with compounds **8**. This may be due to the bulkier tetrasubstituted pyrazole destroys DNA binding and activity. In fact, the compounds having trisubstituted pyrazole (**7**) and disubstituted isoxazole (**9**) units exhibited good activity when compared with the compounds having terasubstituted pyrazole (**8**) unit. It was observed that the presence of chloro substituent enhances the activity. The compounds **7c** and **9c** displayed excellent activity against Gram-positive bacteria (inhibitory zone > 28 mm) and good activity against Gram-negative bacteria (inhibitory zone > 22 mm). All the test compounds showed moderate to high inhibitory effect towards tested fungi (**Table 4**).

The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (**Table 5**). The structure-antimicrobial activity relationship of the tested compounds revealed that disubstituted pyrazole and trisubstituted isoxazole in

Table 3. The *in vitro* antibacterial activity of compounds 2, 3, 7-9.

Compd	Concentration (μg/ml)	Zone of inhibition (mm)			
		Gram (+)ve		Gram (-)ve	
		S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
2a	100	10	9	-	-
	200	12	11	-	-
2b	100	8	9	-	-
	200	10	11	-	-
2c	100	13	11	18	9
	200	15	14	19	11
3a	100	12	13	-	-
	200	15	15	10	-
3b	100	10	09	-	-
	200	12	12	-	-
3c	100	15	14	11	12
	200	18	17	13	14
7a	100	25	22	19	18
	200	28	24	22	20
7b	100	19	20	18	16
	200	21	23	20	19
7c	100	30	28	22	20
	200	32	31	25	23
8a	100	16	15	15	14
	200	18	17	17	17
8b	100	15	16	10	12
	200	17	18	13	14
8c	100	19	19	15	14
	200	21	21	17	17
9a	100	23	21	18	18
	200	25	24	20	19
9b	100	22	20	17	15
	200	24	23	19	17
9c	100	27	25	21	20
	200	29	28	24	23
Chloraphenicol	100	35	38	37	42
	200	41	44	42	45

Table 4. The *in vitro* antifungal activity of compounds 2, 3, 7-9.

Compd	Concentration (μg/ml)	Zone of inhibition (mm)		
		F. solani	*C. lunata*	*A. niger*
2a	100	17	13	12
	200	21	16	14
2b	100	15	12	10
	200	18	14	13
2c	100	17	17	15
	200	20	21	19
3a	100	16	13	10
	200	18	14	13
3b	100	14	10	9
	200	15	12	12
3c	100	18	16	14
	200	20	19	17
7a	100	29	26	22
	200	32	32	24
7b	100	26	26	23
	200	30	31	26
7c	100	33	32	27
	200	35	36	29
8a	100	17	17	14
	200	20	21	17
8b	100	16	16	15
	200	19	20	18
8c	100	17	18	17
	200	21	21	20
9a	100	25	26	23
	200	27	29	26
9b	100	22	23	19
	200	26	25	23
9c	100	28	28	26
	200	32	30	29
Ketoconazole	100	38	41	36
	200	42	44	39

combination with pyrrole displayed greater activity. The compounds having tetrasubstituted pyrazole with pyrrole exhibited least activity. The maximum activity wasobserved with the compounds **7c** and **9c**.

4. Experimental Section

Melting points were determined in open glass capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were run in $CDCl_3$/DMSO-d_6 on a Jeol JNM spectrometer operating at 400 and 100 MHz. All chemical shifts were reported in δ ppm using TMS as an internal standard. The elemental analyses were determined on a Perkin-Elmer 24˚C elemental analyzer. The starting material 1-aroyl-2-styrylsulfonylethene (**1**) was prepared by the literature procedure [24].

Method 1:

General procedure for the synthesis of 4-aroyl-3-(phenylethenesulfonyl)-1*H*-pyrrole (**2**)/4-aroyl-3-(4'-phenyl-1'*H* -pyrrol-3'-ylsulfonyl)-1*H*-pyrrole (**3**)

A mixture of **1** (0.5 mmol) and TosMIC (1 mmol) in Et_2O-DMSO (2:1) was added dropwise under stirring to a suspension of NaH (2 mmol) in Et_2O (10 mL) at room temperature and stirring was continued for 5 - 6 hr. Then, water was added and the reaction mass was extracted with Et_2O. The ethereal fraction was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The resulting mixture was separated by column chromatography (hexane-ethyl acetate; 4:1) and identified as 4-aroyl-3-(phenylethenesulfonyl)-1*H*-pyrrole (**2**) (major) and 4-aroyl-3-(4'-phenyl-1'*H*-pyrrole-3'-ylsulfonyl)-1*H*-pyrrole (**3**) (minor).

Method 2:

General procedure for the synthesis of 4-aroyl-3-(4'-phenyl-1'*H*-pyrrol-3'-ylsulfonyl)-1*H*-pyrrole (**3**)

A solution of **1** (1 mmol) and TosMIC (4 mmol) in Et_2O-DMSO (2:1) was added dropwise under stirring to a suspension of NaH (4 mmol) in Et_2O (20 mL) at RT and stirring was continued for about 3 - 4 hr. Then, water was added and the reaction mass extracted with Et_2O. The ethereal layer was dried (an. Na_2SO_4) and the solvent was removed *in vacuo*. The solid obtained was purified by column chromatography (ethyl acetate/hexane, 1:4).

Method 3:

The compound **3** was also obtained by adding an equimolar (5 mmol) mixture of **2** and TosMIC in Et_2O-DMSO (2:1) dropwise under stirring to a suspension of NaH (1 mmol) in Et_2O (6 mL) at RT. Stirring was continued for 4 - 5 hr. Then, the contents were diluted with water and extracted with Et_2O. The ethereal layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent

Table 5. Minimum inhibitory concentration of compounds 7c and 9c.

Compd	Minimum inhibitory concentration (MIC), μg/ml						
	S. aureus	*B. subtilis*	*E. Coli*	*K. pneumoniae*	*F. solani*	*C. lunata*	*A. niger*
7c	50	50	100	50	25	12.5	50
9c	100	100	100	100	100	50	100
Chloramphenicol	6.25	6.25	6.25	12.5	-	-	-
Ketoconazole	-	-	-	-	12.5	6.25	6.25

under vacuum resulted in a solid which was purified by column chromatography (ethyl acetate/hexane, 1:4).

General procedure for the synthesis of 4-aroyl-3-(4'-phenyl-4',5'-dihydro-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**4**)

To a cooled solution of **2** (5 mmol) in dichloromethane (20 mL), an ethereal solution of diazomethane (40 ml, 0.4 M) and triethylamine (0.12 g) were added. The reaction mixture was kept at –20 to –15 ˚C for 40 - 48 hr. The solvent was removed under reduced pressure and the resultant solid was recrystallized from 2-pro- panol.

General procedure for the synthesis of 4-aroyl-3-(1',5'-diphenyl-3'-aryl-4',5'-dihydro-1'*H*-pyrazol-4-yl-sulfonyl)-1*H*-pyrrole (**5**)

A mixture of **2** (1 mmol), araldehyde phenylhydrazone (2 mmol) and chloramine-T (2 mmol) in methanol (15 mL) was refluxed for 16 - 18 hr on a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product which was recrystallized from ethanol.

General procedure for the synthesis of 4-aroyl-3-(3'-aryl-5'-phenyl-4',5'-dihydroisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (**6**)

The compound **2** (1 mmol), araldoxime (2 mmol) and chloramine-T (2 mmol) in methanol (20 mL) was refluxed for 14-16 hr on a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The solid obtained was purified by recrystallization from ethanol.

General procedure for the synthesis of 4-aroyl-3-(4'-phenyl-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**7**)/4-aroyl-3-(1',5'-diphenyl-3'-aryl-1'*H*-pyrazol-4'-yl-sulfonyl)-1*H*-pyrrole (**8**)/4-aroyl-3-(3'-aryl-5'-phenylisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (**9**)

A solution of **4**-**6** (1 mmol) and chloranil (1.4 mmol) in xylene (10 mL) was refluxed for 25 - 30 hr. Then, the reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was then dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The resultant solid was purified by recrystallization from methanol.

5. Conclusions

A new class of bis heterocycles 4-aroyl-3-(4'-phenyl-1'*H*-pyrazol-3'-ylsulfonyl)-1*H*-pyrrole (**7**), 4-aro-yl-3-(1',5'-diphenyl-3'-aryl-1'*H*-pyrazol-4'-ylsulfonyl)-1*H*-pyrrole (**8**) and 4-aroyl-3-(3'-aryl-5'-phenylisoxazol-4'-ylsulfonyl)-1*H*-pyrrole (**9**) were prepared by the regioselective reaction of tosylmethyl isocyanide and 1,3-dipolar cycloaddtion reaction of diazomethane, nitrile imines and nitrile oxides with 1-aroyl-2-styrylsulfonylethene (**1**). The antimicrobial testing showed that the compounds **7c** and **9c** exhibited greater antimicrobial activity.

6. Acknowledgements

The authors are thankful to UGC, New Delhi, India for financial assistance under major research project.

7. References

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