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Potent Antibacterial Agents: *N*-Substituted Derivatives of *N*-(4-Methylpyridin-2-yl)benzenesulfonamide

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In the present work, a new series of *N*-substituted-*N*-(4-methylpyridin-2-yl)benzenesulfonamides (**5a-f**), was synthesized and evaluated for antibacterial activity. The synthesis was carried out by the coupling of 2-amino-4-methylpyridine (**1**) with benzenesulfonyl chloride (**2**) yielded *N*-(4-methylpyridin-2-yl)benzenesulfonamide (**3**) under dynamic pH control of basic aqueous medium of sodium carbonate. Further, the molecule **3** was reacted with different alkyl/aralkyl halides, **4a-f**, yielded the products **5a-f**, in the presence of *N,N*-dimethyl formamide and LiH. The proposed structures of synthesized molecules were corroborated by IR, ^{1}H NMR and EI-MS spectral data and also screened for antibacterial activity. All the compounds exhibited moderately good inhibitors and only compound **5e** executed no activity against *P. aeroginosa*, gram-negative bacterial strain.

Keywords: 2-Amino-4-methylpyridine, Antibacterial activity, Sulfonamide, ^{1}H NMR and EI-MS.

INTRODUCTION

Sulfonamides have much importance in medicinal chemistry because of various biological activities[1-4] such as antibacterial[5], hypoglycemic[6], diuretic[7], anticarbonic anhydrase, antithyroid *in vitro* and *in vivo*, antiinflammatory[8,9], anticancer, antihypertensive[10] and anticonvulsing activities; as well as potential herbicidal properties for agricultural applications[11]. Although new methodologies have been introduced yet the ceremonious preparation by stirring of amino compounds and sulfonyl halides is still in practice[12]. Environmentally benignant sulfonamides have been synthesized at room temperature in water under pH control with Na_2CO_3[13,14]. The action of sulfonamides, as drug, is relied on their structural compatibility with *p*-amino benzoic acid which inhibits the folic acid formation required by bacteria[15,16].

In continuation of our area of interest[17,18], here the synthesis of various *N*-substituted sulfonamides derived from 2-amino-4-methylpyridine is reported along with their antibacterial activity. The minimum inhibitory concentration (MIC) values rendered these molecules moderately good inhibitors.

EXPERIMENTAL

Thin layer chromatography (TLC) monitored the purity of compounds using solvent systems of ethyl acetate and *n*-hexane. TLC were developed on pre-coated silica gel G-25-UV_{254} plates and visualized under 254 nm. The melting points were computed on Gallonkamp apparatus by open capillary tube and were uncorrected. Infrared spectra were recorded in KBr pellet on a Jasco-320-A spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker spectrometer using MeOD as solvent. Chemical shifts are given in parts per million (ppm) and coupling constant in Hertz (Hz). Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer, with a data system.

Synthesis of *N*-(4-methylpyridin-2-yl)benzenesulfonamide (3): 2-Amino-4-methylpyridine (**1**; 0.02 mol) was suspended in 50 mL distilled water in a 250 mL round bottom flask followed by the addition of equimolar benzenesulfonyl chloride (**2**). Solid Na_2CO_3 was added to control pH of the reaction mixture between 8 and 10. The reaction contents were stirred for 3-4 h along with monitoring by TLC. After single spot, few drops of concentrated HCl were added gradually until the acidity was about pH 3-5. The precipitates were collected by filtration and washed by distilled water. The title compound was yielded on re-crystallization from methanol. White amorphous powder; Yield: 86 %; m.p.: 150-152 °C; m.f.: $C_{12}H_{12}N_2O_2S$; molar mass: 248 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3452 (N-H), 3060 (aromatic C-H), 1640 (aromatic C=C), 1605 (aromatic C=N), 1337 (S=O); ^{1}H NMR (MeOD, 300 MHz,

δ/ppm): 8.01 (d, *J* = 7.2 Hz, 1H, H-6), 7.94 (dd, *J* = 8.7, 1.2 Hz, 2H, H-2' & H-6'), 7.83-7.80 (m, 1H, H-4'), 7.55 (t, *J* = 7.8 Hz, 2H, H-3' & H-5'), 7.14 (s, 1H, H-3), 7.09 (d, *J* = 7.2 Hz, 1H, H-5), 2.40 (s, 3H, CH_3-4); EIMS (*m/z*): 248 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 107 $[C_6H_7N_2]^+$, 92 $[C_6H_6N]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$.

General procedure for the synthesis of *N*-substituted sulfonamides (5a-f): The calculated amount of molecule **3** (0.8 mmol) was completely dissolved in 10 mL DMF and was activated by lithium hydride (0.5 mmol). The alkyl/aralkyl halides (0.8 mmol) were added to the mixture after stirring for 30-35 min. The reaction contents were further stirred for 5-6 h and monitored through TLC. At the end of reaction, ice cold distilled water was added and the title products were separated through solvent extraction using chloroform for liquids and filtration for solids.

***N*-(Propan-1-yl)-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5a):** Brownish yellow liquid; Yield: 75 %; m.f.: $C_{15}H_{18}N_2O_2S$; molar mass: 290 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3050 (Aromatic C-H), 1630 (Aromatic C=C), 1595 (Aromatic C=N), 1335 (S=O); ^{1}H NMR (MeOD, 300MHz, δ/ppm): 7.99 (d, *J* = 7.5 Hz, 1H, H-6), 7.88 (dd, *J* = 8.4, 1.5 Hz, 2H, H-2' & H-6'), 7.79-7.73 (m, 1H, H-4'), 7.53 (t, *J* = 7.2 Hz, 2H, H-3' & H-5'), 7.19 (s, 1H, H-3), 7.14 (d, *J* = 7.5 Hz, 1H, H-5), 3.22 (t, *J* = 6.9 Hz, 2H, H-1''), 2.38 (s, 3H, CH_3-4), 1.89-1.85 (m, 2H, H-2''), 1.03 (t, *J* = 6.9 Hz, 3H, CH_3-3''); EIMS (*m/z*): 290 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 107 $[C_6H_7N_2]^+$, 92 $[C_6H_6N]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$, 43 $[C_3H_7]^+$.

***N*-(Propan-2-yl)-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5b):** Pale yellow liquid; Yield: 81 %; m.f.: $C_{15}H_{18}N_2O_2S$; molar mass: 290 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3058 (aromatic C-H), 1635 (aromatic C=C), 1602 (aromatic C=N), 1339 (S=O); ^{1}H NMR (MeOD, 300 MHz, δ/ppm): 7.98 (d, *J* = 7.2 Hz, 1H, H-6), 7.88 (dd, *J* = 7.5, 1.2 Hz, 2H, H-2' & H-6'), 7.80-7.73 (m, 1H, H-4'), 7.51 (t, *J* = 7.5 Hz, 2H, H-3' & H-5'), 7.21 (s, 1H, H-3), 7.15 (d, *J* = 7.2 Hz, 1H, H-5), 4.19-4.11 (m, 1H, H-1''), 2.41 (s, 3H, CH_3-4), 1.03 (d, *J* = 6.9 Hz, 6H, CH_3-2'' & CH_3-3''); EIMS (*m/z*): 290 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 107 $[C_6H_7N_2]^+$, 92 $[C_6H_6N]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$, 43 $[C_3H_7]^+$.

***N*-(Butan-1-yl)-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5c):** Light brown liquid; Yield: 79 %; m.f.: $C_{16}H_{20}N_2O_2S$; molar mass: 304 g/mol; IR (KBr, ν_{max}, cm^{-1}): 2959 (aromatic C-H), 1639 (aromatic C=C), 1546 (aromatic C=N), 1335 (S=O); ^{1}H NMR (MeOD, 300 MHz, δ/ppm): 8.05 (d, *J* = 7.2 Hz, 1H, H-6), 7.95 (d, *J* = 7.5 Hz, 2H, H-2' & H-6'), 7.81-7.76 (m, 1H, H-4'), 7.59 (t, *J* = 7.2 Hz, 2H, H-3' & H-5'), 7.21 (s, 1H, H-3), 7.10 (d, *J* = 7.2 Hz, 1H, H-5), 3.29 (t, *J* = 6.9 Hz, 2H, H-1''), 2.41 (s, 3H, CH_3-4), 1.92-1.87 (m, 4H, H-2'' & H-3''), 1.01 (t, *J* = 6.9 Hz, 3H, CH_3-4''); EIMS (*m/z*): 304 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 107 $[C_6H_7N_2]^+$, 92 $[C_6H_6N]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 57 $[C_4H_9]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$.

***N*-Benzyl-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5d):** Dark brown sticky solid; Yield: 77 %; m.f.: $C_{19}H_{18}N_2O_2S$; molar mass: 338 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3063 (aromatic C-H), 1649 (aromatic C=C), 1601 (aromatic C=N), 1335 (S=O); ^{1}H NMR (MeOD, 300 MHz, δ/ppm): 7.97 (d, *J* = 7.2 Hz, 1H, H-6), 7.64 (dd, *J* = 7.5, 3.0 Hz, 2H, H-2' & H-6'), 7.55-7.50 (m, 1H, H-4'), 7.37 (d, *J* = 7.2 Hz, 2H, H-3' & H-5'), 7.31-7.28 (m, 5H, H-2'' to H-6''), 7.23 (d, *J* = 2.7 Hz, 1H, H-3), 6.64 (dd, *J* = 7.2, 1.5 Hz, 1H, H-5), 5.39 (s, 2H, H-7''), 2.27 (s, 3H, CH_3-4); EIMS (*m/z*): 338 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 107 $[C_6H_7N_2]^+$, 92 $[C_6H_6N]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 65 $[C_5H_5]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$.

***N*-(2-Chlorobenzyl)-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5e):** Brown liquid; Yield: 83 %; m.f.: $C_{19}H_{17}N_2O_2SCl$; molar mass: 372 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3062 (aromatic C-H), 1644 (aromatic C=C), 1603 (aromatic C=N), 1333 (S=O); ^{1}H NMR (MeOD, 300 MHz, δ/ppm): 8.03 (d, *J* = 7.2 Hz, 1H, H-3''), 7.93 (d, *J* = 7.2 Hz, 2H, H-2' & H-6'), 7.65 (d, *J* = 7.2 Hz, 1H, H-6), 7.49-7.43 (m, 1H, H-4'), 7.39 (t, *J* = 7.5 Hz, 1H, H-5''), 7.36 (t, *J* = 7.5 Hz, 2H, H-3' & H-5'), 7.33 (t, *J* = 7.2 Hz, 1H, H-4''), 7.25 (d, *J* = 8.1 Hz, 1H, H-6''), 7.21 (s, 1H, H-3), 6.73 (dd, *J* = 7.2, 1.2 Hz, 1H, H-5), 5.30 (s, 2H, H-7''), 2.27 (s, 3H, CH_3-4); EIMS (*m/z*): 372 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 125 $[C_7H_6Cl]^+$, 107 $[C_6H_7N_2]^+$, 99 $[C_5H_4Cl]^+$, 92 $[C_6H_6N]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 65 $[C_5H_5]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$.

***N*-(4-Chlorobenzyl)-*N*-(4-methylpyridin-2-yl)benzenesulfonamide (5f):** Brown amorphous powder; Yield: 79 %; m.p.: 128 °C; m.f.: $C_{19}H_{17}N_2O_2SCl$; molar mass: 372 g/mol; IR (KBr, ν_{max}, cm^{-1}): 3060 (aromatic C-H), 1641 (aromatic C=C), 1606 (aromatic C=N), 1331 (S=O); ^{1}H NMR (MeOD, 300 MHz, δ/ppm): 7.96 (d, *J* = 7.5 Hz, 1H, H-6), 7.62 (d, *J* = 7.2 Hz, 2H, H-2' & H-6'), 7.51-7.46 (m, 1H, H-4'), 7.40 (t, *J* = 7.5 Hz, 2H, H-3' & H-5'), 7.35 (s, 1H, H-3), 7.27 (d, *J* = 8.7 Hz, 2H, H-3'' & H-5''), 7.20 (d, *J* = 8.4 Hz, 2H, H-2'' & H-6''), 6.66 (dd, *J* = 7.5, 1.2 Hz, 1H, H-5), 5.34 (s, 2H, H-7''), 2.28 (s, 3H, CH_3-4); EIMS (*m/z*): 372 $[M]^+$, 141 $[C_6H_5SO_2]^+$, 125 $[C_7H_6Cl]^+$, 107 $[C_6H_7N_2]^+$, 99 $[C_5H_4Cl]^+$, 92 $[C_6H_6N]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 66 $[C_5H_6]^+$, 65 $[C_5H_5]^+$, 52 $[C_3H_2N]^+$, 51 $[C_4H_3]^+$.

Antibacterial activity: The antimicrobial activity was determined following the principle that increased absorbance of broth medium is directly related to log phase of growth and was performed in sterile 96-wells microplates under aseptic conditions[19,20]. Four gram-negative (*Salmonella typhi*, *Escherichia coli*, *Klebsiella pneumonae* and *Pseudomonas aeruginosa*) and two gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) were included in the study and were maintained on stock culture agar medium. The test samples (with suitable solvents and dilutions) 20 µg/well and 180 µL fresh bacterial culture (with suitable dilution by fresh nutrient broth) was poured into wells to make a volume of 200 µL.

The initial absorbance of the culture was kept 0.12-0.19 at 540 nm. The absorbance was measured at 540 nm using microplate reader, before and after incubation at 37 °C for 16-24 h with lid on the microplate. The difference was related to bacterial growth. The per cent inhibition was calculated using the formula:

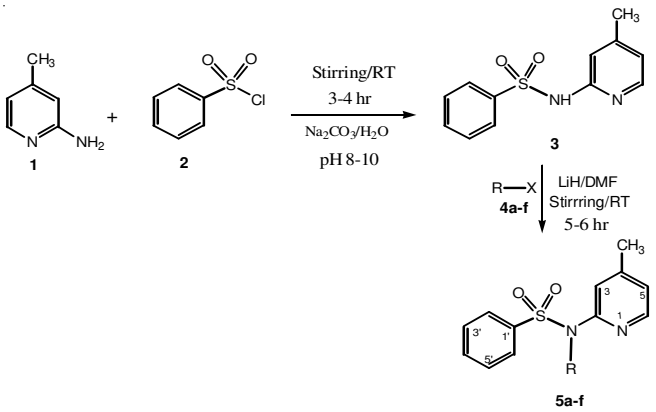
$$\text{Inhibition (\%)} = 100 - \frac{\text{Absorbance of test sample}}{\text{Absorbance of control}} \times 100$$

Results are mean of triplicate (n = 3, ± sem). Ciprofloxacin was taken as reference standard. Minimum inhibitory concentration was measured with suitable dilutions (5-30 µg/well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software.

Statistical analysis: All the measurements were accounted in triplicate and statistical analysis was performed by Microsoft Excel 2010. Results are presented as mean ± sem.

RESULTS AND DISCUSSION

Present research work was an attempt to develop a new series of biological active compounds which may be helpful in drug development program. The first step yielded the molecule, *N*-(4-methylpyridin-2-yl)benzenesulfonamide (**3**) from 2-amino-4-methylpyridine (**1**) and benzenesulfonyl chloride (**2**) in an alkaline aqueous medium in good percentage yield as described in **Scheme-I**. The product was accomplished after increasing the acidity of reaction contents up to pH 3-5 after stirring for 3-4 h and isolated through filtration. Although acid is mandatory for better yield yet excess of it has negative effect. The product **3** was further employed to accomplish *N*-substituted-*N*-(4-methylpyridin-2-yl)benzenesulfonamides (**5a-f**) by its reaction with alkyl/aralkyl halides in LiH/DMF. The target compounds were isolated through solvent extraction or filtration. The sulfonamide **3** was precipitated as white amorphous powder with 86 % yield and 150-152 °C melting point. The EI-MS showed the $[M]^{+\bullet}$ ion peak at *m/z* 248 owing to molecular formula as $C_{12}H_{12}N_2O_2S$. The molecular formula was also underpinned by integration ratio of protons in ^{1}H NMR spectrum. The three signals appearing at δ 7.94 (dd, *J* = 8.7, 1.2 Hz, 2H, H-2' & H-6'), 7.83-7.80 (m, 1H, H-4') and 7.55 (t, *J* = 7.8 Hz, 2H, H-3' & H-5') were assigned to the protons of benzenesulfonyl group. The other signals resonating at δ 8.01 (d, *J* = 7.2 Hz, 1H, H-6), 7.14 (s, 1H, H-3), 7.09 (d, *J* = 7.2 Hz, 1H, H-5) and 2.40 (s, 3H, CH_3-4) confirmed the presence of 2,4-disubstituted pyridine ring. All the functional groups in the molecule were supported by IR and the structure by EI-MS data. All these evidences assigned the structure of **3**



Compd.	-R	Compd.	-R
5a	—CH_2—CH_2—CH_3 (1" 2" 3")	5d	7" H_2C on phenyl (1" 3" 5")
5b	3" CH_3 —CH—CH_3 (1" 2")	**5e**	Cl, 7" H_2C on phenyl (1" 3" 5")
5c	—CH_2—CH_2—CH_2—CH_3 (1" 2" 3" 4")	**5f**	7" H_2C on phenyl (1" 3" 5") Cl

as *N*-(4-methylpyridin-2-yl)benzenesulfonamide collectively. Similarly the structures of other synthesized molecules were corroborated on the basis of spectral evidences of IR, ^{1}H NMR and EI-MS.

Antibacterial activity (*in vitro*): The screening of the synthesized molecules against gram-bacteria explored that all were potent inhibitors except **5e** which executed no potential against *P. aeroginosa*, as evident from the MIC values (Table-2). Among these molecules, the molecule, **5b**, was the most active inhibitor against *K. pneumonae* with MIC value of 9.49 ± 3.16

TABLE-1
%AGE INHIBITION VALUES OF ANTIBACTERIAL ACTIVITY

Compound	%Age inhibition					
	S. typhi (-)	*E. coli* (-)	*K. pneumonae* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
3	62.89 ± 2.58	72.33 ± 1.33	67.33 ± 1.65	71.30 ± 2.22	67.06 ± 1.39	77.09 ± 0.45
5a	61.39 ± 1.91	67.78 ± 3.56	61.42 ± 2.67	52.45 ± 2.55	63.71 ± 3.71	70.23 ± 1.95
5b	65.88 ± 1.34	67.39 ± 0.72	63.52 ± 4.43	56.20 ± 1.20	64.74 ± 2.37	72.64 ± 2.55
5c	52.63 ± 2.84	60.22 ± 2.44	55.28 ± 2.78	58.59 ± 4.13	55.00 ± 3.35	66.95 ± 2.23
5d	55.46 ± 0.10	67.72 ± 2.50	61.53 ± 1.19	63.80 ± 3.67	56.55 ± 4.07	74.86 ± 4.05
5e	58.87 ± 0.93	59.00 ± 1.33	56.70 ± 1.82	45.72 ± 2.77	62.11 ± 1.08	67.55 ± 0.45
5f	68.66 ± 3.15	67.17 ± 0.72	67.61 ± 1.02	66.52 ± 3.57	66.96 ± 0.98	74.73 ± 0.55
Ciprofloxacin	89.71 ± 1.43	88.76 ± 1.94	91.32 ± 0.54	88.95 ± 2.05	90.10 ± 0.77	90.00 ± 1.23

TABLE-2
MIC VALUES OF ANTIBACTERIAL ACTIVITY

Compound	MIC					
	S. typhi (-)	*E. coli* (-)	*K. pneumonae* (-)	*P. aeroginosa* (-)	*B. subtilis* (+)	*S. aureus* (+)
3	14.92 ± 3.02	15.99 ± 0.14	11.72 ± 2.68	14.99 ± 1.81	12.08 ± 3.15	14.06 ± 1.17
5a	14.82 ± 2.02	14.67 ± 1.03	13.39 ± 2.24	19.19 ± 2.70	10.81 ± 3.18	13.09 ± 2.07
5b	13.36 ± 2.06	13.08 ± 3.74	9.49 ± 3.16	18.50 ± 3.89	11.57 ± 3.90	13.60 ± 3.67
5c	18.92 ± 2.00	17.81 ± 4.71	15.44 ± 3.34	17.85 ± 4.11	15.87 ± 3.11	14.76 ± 3.50
5d	17.05 ± 1.50	16.23 ± 2.16	10.13 ± 2.32	16.64 ± 1.17	14.42 ± 2.40	13.74 ± 2.43
5e	17.95 ± 1.11	18.10 ± 3.21	16.02 ± 1.59	-	12.07 ± 2.21	16.51 ± 4.73
5f	14.76 ± 2.71	15.52 ± 3.50	10.35 ± 1.05	17.00 ± 2.96	12.69 ± 1.06	15.10 ± 3.30
Ciprofloxacin	9.66 ± 1.08	9.27 ± 0.58	8.34 ± 1.50	9.61 ± 2.08	9.61 ± 2.08	9.20 ± 2.31

Note: Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/ well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software

μM relative to the reference standard, ciprofloxacin, having MIC value of 8.34 ± 1.50 μM. All the compounds executed almost the 50 % inhibitory action against all the bacterial strains with some exceptions, relative to the reference standard. The percentagbe inhibition and MIC values of the synthesized molecules relative to ciprofloxacin are shown in Tables 1 and 2, respectively.

Conclusion

The structures of the synthesized compounds are well characterized by spectroscopic data. The newly synthesized compounds showed varying degree of antibacterial activity.

REFERENCES

1. A. Camargo-Ordoñez, C. Moreno-Reyes, F. Olazarán-Santibáñez, S. Martínez-Hernández, V. Bocanegra-García and G. Rivera, *Quim. Nova*, **34**, 787 (2011).
2. A. Ali, G.S.K.K. Reddy, H. Cao, S.G. Anjum, M.N.L. Nalam, C.A. Schiffer and T.M. Rana, *J. Med. Chem.*, **49**, 7342 (2006).
3. A.J. McCarroll, T.D. Bradshaw, A.D. Westwell, C.S. Matthews and M.F.G. Stevens, *J. Med. Chem*., **50**, 1707 (2007).
4. B.L. Wilkinson, L.F. Bornaghi, T.A. Houston, A. Innocenti, D. Vullo, C.T. Supuran and S.-A. Poulsen, *J. Med. Chem*., **50**, 1651 (2007).
5. J. Drews, *Science*, **287**, 1960 (2000).
6. A.E. Boyd, *Diabetes*, **37**, 847 (1988).
7. C.T. Supuran and A. Scozzafava, *Expert Opin. Ther. Patents*, **10**, 575 (2000).
8. A.A. Kadi, N.R. El-Brollosy, O.A. Al-Deeb, E.E. Habib, T.M. Ibrahim and A.A. El-Emam, *Eur. J. Med. Chem*., **42**, 235 (2007).
9. S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, A. Ranise, W. Filippelli, B. Rinaldi, A. Capuano and G. Falcone, *Bioorg. Med. Chem*., **14**, 1698 (2006).
10. M.M. Ghorab, F.A. Ragab, H.I. Heiba and R.M. El-Hazek, *Eur. J. Med. Chem*., **46**, 5120 (2011).
11. J.P. Liou, K.S. Hsu, C.C. Kuo, C.Y. Chang and J.Y. Chang, *J. Pharmacol. Exp. Ther*., **323**, 398 (2007).
12. (a) S.W. Wright and K.N. Hallstrom, *J. Org. Chem*., **71**, 1080 (2006).; (b) A.R. Katritzky, A.A.A. Abdel-Fattah, A.V. Vakulenko and H. Tao, *J. Org. Chem*., **70**, 9191 (2005).
13. X. Deng and N.S. Mani, *Green Chem*., **8**, 835 (2006).
14. M. Jafarpour, A. Rezaeifard and T. Golshani, *J. Phosphorous Sulfur Silicon Rel. Elem*., **186**, 140 (2010).
15. A. Thakur, M. Thakur and P.V. Khadikar, *ARKIVOC*, 87 (2006).
16. A. Alsughayer, A.Z.A. Elassar, S. Mustafa and F. Al-Sagheer, *J. Biomater. Nanobiotechnol*., **2**, 143 (2011).
17. H. Khalid, Aziz-ur-Rehman, M.A. Abbasi and K.M. Khan, *J. Pharm. Pharm. Sci*., **4**, 443 (2012).
18. Aziz-ur-Rehman, S. Afroz, M.A. Abbasi, W. Tanveer, K.M. Khan, M. Ashraf, I. Afzal and N. Ambreen, *Pak. J. Pharm. Sci*., **25**, 809 (2012).
19. M. Kaspady, V.K. Narayanaswamy, M. Raju and G.K. Rao, *Lett. Drug Des. Discov*., **6**, 21 (2009).
20. C.-R. Yang, Y. Zhang, M.R. Jacob, S.I. Khan, Y.-J. Zhang and X.-C. Li, *Antimicrob. Agents Chemother*., **50**, 1710 (2006).