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Original article

Synthesis and antioxidant activity of oxazolyl/thiazolylsulfonylmethyl pyrazoles and isoxazoles

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ABSTRACT

A new class of oxazolyl/thiazolylsulfonylmethyl pyrazoles (**10**–**13**) and isoxazoles (**14, 15**) were prepared from the synthetically vulnerable intermediate *E*-styrylsulfonylacetic acid methyl ester (**1**) and studied their antioxidant activity.

1. Introduction

The recent literature is enriched with progressive findings about the synthesis and pharmacological activities of azole based compounds. The thiazole ring is an interesting building block in a variety of natural products and bioactive compounds useful as pharmaceuticals or agrochemical agents [1–5]. Recently, many natural products containing thiazole moiety were isolated and most of them exhibit considerable cytotoxicities and antitumor potentials [6–13]. Tiazofurin, a thiazole-4-carboxamide derivative, a C-nucleoside having significant activity against both human lymphoid [14] and lung tumor cell lines [15]. Its biological effects also include its efficiency in the treatment of acute myeloid leukemia [16] and chronic myeloid leukemia in blast crisis [17]. Isoxazoles and pyrazoles have attracted much attention since they play vital role in synthetic organic chemistry over the years and are important bioactive compounds as anti-cancer [18–20], antiviral [21], anti-inflammatory [22], antidiabetic [23], antibacterial and antifungal agents [24–26]. The recent success of pyrazole-based COX-II inhibitors and their application in medicinal chemistry have amplified the importance of pyrazoles [27]. Several pharmaceutical drugs including celecoxib [27] and rimonabant [28] possess the pyrazoles as their core molecular entity [29–31]. The oxazole ring is a useful structural motif found in numerous biologically active molecules. Natural product Hennoxazole A, first isolated from the marine sponge, displays predominant antiviral activity against herpes simplex type I [32]. With this background and to broaden the scope of the ongoing research on developing new and novel bis heterocycles, we planned to synthesize and to investigate the antioxidant potentiality of sulfonylmethyl linked oxazolyl and thiazolyl pyrazoles and isoxazoles.

2. Chemistry

The synthetic intermediate, *E*-styrylsulfonylacetic acid methyl ester (**1**) was prepared as follows. The reaction of styrene with sulfuryl chloride under nitrogen atmosphere produced *E*-styrylsulfonyl chloride. Treatment of latter compound with sodium bicarbonate and sodium sulfite produced the salt, sodium *E*-styryl sulfinate. This on reaction with chloroacetic acid resulted in *E*-styrylsulfonylacetic acid which on esterification with methanol in the presence of conc. H_2SO_4 gave the compound **1** [33]. The two reactive sites, olefin moiety and ester functionality in **1** were conveniently utilized to construct different azole rings. The one-pot reaction of **1** with 2-aminoethanol in the presence of samarium chloride and *n*-butyllithium resulted in 2-(2-arylethenesulfonylmethyl)-4,5-dihydrooxazole (**2**). Similarly the compound 2-(2-arylehenesulfonylmethyl)-4,5-dihydrothiazole (**3**) was prepared by treating **1** with 2-aminoethanethiol (Scheme 1). The compounds**2a** and **3a** in ^{1}H NMR spectra displayed two triplets at 4.25, 4.31 and 4.42, 3.47 due to C_4-H and C_5-H, a singlet at 4.12 and 4.02

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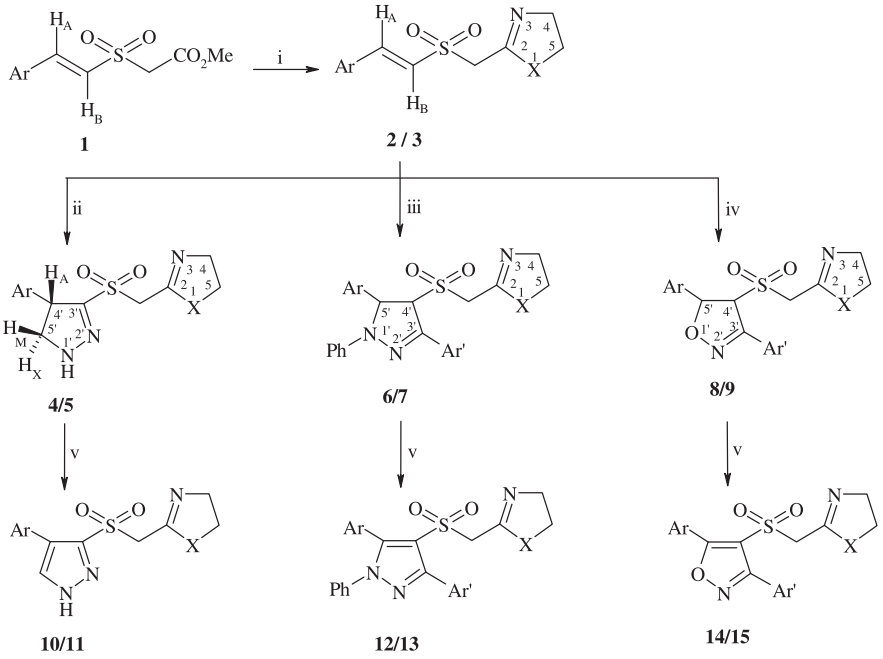

Scheme 1. Synthesis of oxazolyl/thiazolylsulfonylmethyl pyrazoles and isoxazoles.

due to methylene protons. Apart from this, a doublet was observed at 6.57 in **2a** and at 6.50 ppm in **3a** due to olefin proton H_B, while the other, H_A merged with aromatic protons. The 1,3-dipolar cycloaddition is a facile and an elegant method to exploit activated olefins to develop pyrazoles and isoxazoles in the presence of appropriate dipolar reagents. The cycloaddition of ethereal diazomethane to **2** and **3** in the presence of triethylamine at −20 to −15 °C gave 2-(4′,5′-dihydro-4′-aryl-1′*H*-pyrazol-3′-ylsulfonylmethyl)-4,5-dihydrooxazole (**4**) and 2-(4′,5′-dihydro-4′-aryl-1′*H*-pyrazol-3′-ylsulfonylmethyl)-4,5-dihydrothiazole (**5**) (Scheme 1). The methine and methylene protons of pyrazoline ring exhibited an AMX splitting pattern in the ^{1}H NMR spectra of **4a** and **5a**. The three double doublets observed at 4.56, 4.24, 3.89 in **4a** and at 4.42, 4.18, 3.78 in **5a** were assigned to H_A, H_M and H_x, respectively. The coupling constant values $J_{AM} = 12.1$ Hz, $J_{Ax} = 6.2$ Hz, $J_{Mx} = 11.0$ Hz in **4a** and $J_{AM} = 11.8$ Hz, $J_{Ax} = 5.9$ Hz, $J_{Mx} = 10.5$ Hz in **5a** indicated that H_A, H_M are *cis*, H_A, H_x are *trans* and H_M, H_x are *geminal*. On the other hand, the cycloaddition of nitrile imines generated from araldehyde phenylhydrazones in the presence of chloramine-T to **2** and **3** resulted in highly substituted pyrazolinyl derivative 2-(4′,5′-dihydro-1′-phenyl-3′,5′-diarylpyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**6**) and 2-(4′,5′-dihydro-1′-phenyl-3′,5′-diarylpyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**7**) (Scheme 1). The ^{1}H NMR spectra of **6a** and **7a** displayed two doublets at 5.21, 5.08 and 5.56, 5.42 ppm due to C_4′-H and C_5′-H, in addition to the signals due to C_4-H, C_5-H and methylene protons. In a much similar way, the cycloaddition of nitrile oxides generated from araldoximes in the presence of chloramine-T to compounds **2** and **3** produced 2-(4′,5′-dihydro-3′,5′-diarylisoxazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**8**) and 2-(4′,5′-dihydro-3′,5′-diarylisoxazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**9**). The ^{1}H NMR spectra of **8a** and **9a** showed two doublets at 5.19, 5.02 and 5.69, 5.49 ppm which were assigned to C_4′-H and C_5′-H, respectively apart from other signals. The aromatization of pyrazoline and isoxazoline rings in **4**–**9** was carried out by treating the respective compounds with chloranil in xylene. Thus the compounds 2-(4′-aryl-1′*H*-pyrazol-3′-ylsulfonylmethyl)-4,5-dihydrooxazole (**10**), 2-(4′-aryl-1′*H*-pyrazol-3′-ylsulfonylmethyl)-4,5-dihydrothiazole (**11**), 2-(1′-phenyl-3′,5′-diarylpyrazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**12**), 2-(1′-phenyl-3′,5′-diarylpyrazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**13**), 2-(3′,5′-diarylisoxazol-4′-ylsulfonylmethyl)-4,5-dihydrooxazole (**14**) and 2-(3′,5′-diarylisoxazol-4′-ylsulfonylmethyl)-4,5-dihydrothiazole (**15**) were prepared. The absence of signals corresponding to pyrazoline and isoxazoline ring protons in **10**–**15** indicated that aromatization took place. The structures of these compounds were further confirmed by IR and ^{13}C-NMR spectra.

3. Biology

3.1. Antioxidant testing

The compounds **4**–**15** are tested for antioxidant property by DPPH [34,35], nitric oxide [36,37] and H_2O_2 [38] methods.

4. Result and discussion

4.1. Antioxidant testing

The compounds **4**–**15** were tested for antioxidant property by 1,1-diphenylpicrylhydrazyl (DPPH) (Table 1), nitric oxide (Table 2) and hydrogen peroxide (Table 3)methods. The compounds **6b**, **8b**, **10b**, **12b**, **14b** showed good radical scavenging activity in all three

Table 1
The *in vitro* antioxidant activity of **4**–**15** in DPPH method.

Compound	Concentration (μg/ml)			
	50	75	100	IC_{50}
4a	–	–	–	–
4b	38.73	43.65	49.78	100.44
4c	–	–	–	–
5a	–	–	–	–
5b	40.85	43.97	48.20	103.73
5c	–	–	–	–
6a	48.21	53.35	57.97	86.25
6b	64.43	70.24	73.81	67.74
6c	–	–	–	–
7a	–	–	–	–
7b	37.46	45.83	51.52	97.04
7c	–	–	–	–
8a	49.37	55.19	57.93	86.31
8b	58.14	63.26	66.52	75.16
8c	–	–	–	–
9a	–	–	–	–
9b	46.82	50.64	58.56	85.38
9c	–	–	–	–
10a	50.10	54.32	60.78	82.26
10b	59.83	63.67	68.95	72.51
10c	–	–	–	–
11a	–	–	–	–
11b	–	–	–	–
11c	–	–	–	–
12a	51.86	56.57	60.62	82.48
12b	65.50	67.63	70.35	71.07
12c	–	–	–	–
13a	–	–	–	–
13b	–	–	–	–
13c	–	–	–	–
14a	61.65	65.76	71.97	69.47
14b	72.94	75.81	79.66	62.76
14c	–	–	–	–
15a	–	–	–	–
15b	–	–	–	–
15c	–	–	–	–
Ascorbic acid	77.15	80.98	83.82	59.65
Blank	–	–	–	–

(–) Showed no scavenging activity.

Table 2
The *in vitro* antioxidant activity of **4**–**15** in nitric oxide method.

Compound	Concentration (μg/ml)		
	50	75	100
4a	–	–	–
4b	45.91	49.72	51.38
4c	–	–	–
5a	–	–	–
5b	43.07	48.56	52.15
5c	–	–	–
6a	46.73	51.44	57.86
6b	59.07	64.86	70.54
6c	–	–	–
7a	–	–	–
7b	39.42	44.85	50.74
7c	–	–	–
8a	53.86	57.23	62.78
8b	61.93	65.87	71.25
8c	–	–	–
9a	–	–	–
9b	48.64	54.12	59.57
9c	–	–	–
10a	50.57	54.67	57.45
10b	59.37	63.51	65.18
10c	–	–	–
11a	–	–	–
11b	–	–	–
11c	–	–	–
12a	54.48	58.95	63.52
12b	61.59	66.64	68.18
12c	–	–	–
13a	–	–	–
13b	–	–	–
13c	–	–	–
14a	56.72	57.31	62.08
14b	68.76	73.03	76.18
14c	–	–	–
15a	–	–	–
15b	–	–	–
15c	–	–	–
Ascorbic acid	78.23	81.46	82.79
Blank	–	–	–

(–) Showed no scavenging activity.

methods due to the presence of electron donating groups such as –Me and –OMe in benzene ring when compared with the standard drug ascorbic acid. The compounds **4b**, **5b**, **6a**, **7b**, **8a**, **9b**, **10a**, **12a**, **13b**, **14a**, **15b** showed moderate antioxidant activity whereas the other compounds displayed no activity. In general, it was observed that aromatized compounds **10**–**15** exhibited greater activity when compared with the respective dihydro compounds **4**–**9**. The compounds isoxazole in combination with oxazoline **14** exhibited greater activity which may be due to the presence of two oxygen atoms than the compounds having pyrazole and oxazoline **10, 12**. The presence of both electron donating methyl and methoxy substituents enhances the activity. The IC_{50} value of the standard ascorbic acid in DPPH method was found to be 59.65 μg/ml at 100 μg/ml whereas the IC_{50} values of the compounds **6b**, **8b**, **10b**, **12b** and **14b** were found to be 67.74, 75.16, 72.51, 71.07 and 62.76 μg/ml, respectively. Further, the analysis of tables **1**, **2** and **3** indicates that radical scavenging activity in DPPH, nitric oxide and hydrogen peroxide methods increases with increase in concentration.

5. Conclusion

A new class of bis heterocycles- oxazolyl/thiazolylsulfonylmethyl pyrazoles and isoxazoles were prepared from the synthetically vulnerable intermediate *E*-styrylsulfonylacetic acid methyl ester and studied their antioxidant activity. It was observed that the compounds having isoxazole in combination with oxazoline exhibited greater antioxidant activity. The presence of electron donating substituents on the aromatic ring enhances the activity.

6. Experimental section

6.1. Chemistry

Melting points were determined in open 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 ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin–Elmer 240C elemental analyzer. The antioxidant property was carried out by using Shimadzu UV-2450 spectrophotometer.

6.1.1. General procedure for the synthesis of 2-(2-arylethenesulfonylmethyl)-4,5-dihydrooxazole (**2a**–**c**)/2-(2-arylethenesulfonylmethyl)-4,5-dihydrothiazole (**3a**–**c**)

To a flask charged with anhydrous samarium chloride (0.1 mmol), dry toluene and aminoalcohol/aminothiol (2 mmol) were added followed by *n*-butyllithium (2.2 mmol) at 0 °C and

Table 3
The *in vitro* antioxidant activity of **4**–**15** in hydrogen peroxide method.

Compound	Concentration (μg/ml)		
	50	75	100
4a	–	–	–
4b	41.26	42.12	46.76
4c	–	–	–
5a	–	–	–
5b	39.84	42.17	45.05
5c	–	–	–
6a	44.37	45.54	48.07
6b	62.47	64.26	67.74
6c	–	–	–
7a	–	–	–
7b	42.61	43.88	47.89
7c	–	–	–
8a	51.72	53.31	56.57
8b	65.93	66.57	70.94
8c	–	–	–
9a	–	–	–
9b	47.51	49.67	52.63
9c	–	–	–
10a	53.34	55.64	58.48
10b	60.71	62.03	65.48
10c	–	–	–
11a	–	–	–
11b	–	–	–
11c	–	–	–
12a	55.57	57.25	59.14
12b	67.58	68.71	72.53
12c	–	–	–
13a	–	–	–
13b	–	–	–
13c	–	–	–
14a	57.23	58.08	60.11
14b	70.02	71.95	77.08
14c	–	–	–
15a	–	–	–
15b	–	–	–
15c	–	–	–
Ascorbic acid	77.68	79.27	83.16
Blank	–	–	–

(–) Showed no scavenging activity.

stirred for 20 min at the same temperature. Then, the reaction mixture was warmed to reflux at 100 °C and *E*-styrylsulfonylacetic acid methyl ester (**1**) (1 mmol) was added to the contents and refluxion was continued for an additional 10–12 h. The suspension was cooled to room temperature and filtered. The filtrate was extracted with chloroform and washed with water. Evaporation of the solvent *in vacuo* resulted in crude product which was purified by passing through column of silica gel (60–120 mesh) using ethyl acetate: hexane (1:3) as eluent.

*6.1.2. General procedure for the synthesis of 2-(4',5'-dihydro-4'-aryl-1'H-pyrazol-3'-ylsulfonylmethyl)-4,5-dihydrooxazole (**4a**–**c**)/2-(4',5'-dihydro-4'-aryl-1'H-pyrazol-3'-ylsulfonylmethyl)-4,5-dihydrothiazole (**5a**–**c**)*

To a well cooled solution of **2/3** (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 h. The solvent was removed under reduced pressure. The solid obtained was purified by column chromatography (silica gel, 60–120 mesh) using ethyl acetate: hexane (1:2.5) as eluent.

*6.1.3. General procedure for the synthesis of 2-(4',5'-dihydro-1'-phenyl-3',5'-diarylpyrazol-4'-ylsulfonylmethyl)-4,5-dihydrooxazole (**6a**–**c**)/2-(4',5'-dihydro-1'-phenyl-3',5'-diarylpyrazol-4'-ylsulfonylmethyl)-4,5-dihydrothiazole (**7a**–**c**)*

A mixture of **2/3** (1 mmol), araldehyde phenylhydrazone (1.2 mmol) and chloramine-T (1.2 mmol) in methanol (20 ml) was refluxed for 20–22 h 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, brine and dried (an. Na_2SO_4). The solvent was removed under *vacuum*. The resultant solid was recrystallized from ethanol.

*6.1.4. General procedure for the synthesis of 2-(4',5'-dihydro-3',5'-diarylisoxazol-4'-ylsulfonylmethyl)-4,5-dihydrooxazole (**8a**–**c**)/2-(4',5'-dihydro-3',5'-diarylisoxazol-4'-ylsulfonylmethyl)-4,5-dihydrothiazole (**9a**–**c**)*

The compound **2/3** (1 mmol), araldoxime (1.2 mmol) and chloramine-T (1.2 mmol) in methanol (20 ml) were refluxed for 16–18 h 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, brine and dried (an. Na_2SO_4). The solvent was removed under reduced pressure. The solid obtained was purified by recrystallization from ethanol.

*6.1.5. General procedure for the synthesis of 2-(4'-aryl-1'H-pyrazol-3'-ylsulfonylmethyl)-4,5-dihydrooxazole (**10a**–**c**)/2-(4'-aryl-1'H-pyrazol-3'-ylsulfonylmethyl)-4,5-dihydrothiazole (**11a**–**c**)/2-(1'-phenyl-3',5'-diarylpyrazol-4'-ylsulfonylmethyl)-4,5-dihydrooxazole (**12a**–**c**)/2-(1'-phenyl-3',5'-diarylpyrazol-4'-ylsulfonylmethyl)-4,5-dihydrothiazole (**13a**–**c**)/2-(3',5'-diarylisoxazol-4'-ylsulfonylmethyl)-4,5-dihydrooxazole (**14a**–**c**)/2-(3',5'-diarylisoxazol-4'-ylsulfonylmethyl)-4,5-dihydrothiazole (**15a**–**c**)*

A solution of **4/5/6/7/8/9** (1 mmol) in xylene (10 ml) and chloranil (1.2 mmol) was refluxed for 25–30 h. Then, it was treated with a 5% sodium hydroxide solution. The organic extract was separated, repeatedly washed with water and dried (an. Na_2SO_4). The solvent was removed *in vacuo*. The resultant solid was recrystallized from 2-propanol.

6.2. Biological assays

6.2.1. Antioxidant testing

The compounds **4**–**15** are tested for antioxidant property by DPPH, nitric oxide and H_2O_2 methods.

6.2.1.1. DPPH radical scavenging activity. The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of 2,2,-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 ml of various concentrations of the test compounds (25, 50, 75, 100 and 250 μg/ml) in methanol were added to 4 ml of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation

$$I\% = [(A\ \text{control} - A\ \text{sample})/A\ \text{blank}] \times 100$$

where A control is the absorbance of the control reaction (containing all reagents except the test compound) and A sample is the absorbance of the test compound. Tests were carried at in triplicate.

6.2.1.2. Nitric oxide (NO) scavenging activity. Nitric oxide scavenging activity was measured by slightly modified methods of Green *et al.* and Marcocci *et al.* Nitric oxide radicals (NO) were generated from sodium nitroprusside. 1 ml of sodium nitroprusside (10 mM) and 1.5 ml of phosphate buffer saline (0.2 M, pH 7.4) were added to different concentrations (25, 50, 75 and 100 μg/ml) of the test compounds and incubated for 150 min at 25 °C. After incubation 1 ml

of the reaction mixture was treated with 1 ml of Griess reagent (1% sulfanilamide, 2% H_3PO_4 and 0.1% naphthylethylenediamine dihydrochloride). The absorbance of the chromatophore was measured at 546 nm. Butylated hydroxyl toluene was used as standard. Nitric oxide scavenging activity was calculated by the following equation

$$\%\ \text{of scavenging} = [(\text{A control} - \text{A sample})/\text{A blank}] \times 100$$

where A control is the absorbance of the control reaction (containing all reagents except the test compound) and A sample is the absorbance of the test compound. Tests were carried at in triplicate.

6.2.1.3. Hydrogen peroxide (H_2O_2) scavenging activity. The H_2O_2 scavenging ability of the test compound was determined according to the method of Ruch *et al.* A solution of H_2O_2 (40 mM) was prepared in phosphate buffer (pH 7.4). 10, 25, 50, 75 &100 μg/ml concentrations of the test compounds in 3.4 ml phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mM). The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated by the following equation

$$\%\ \text{of scavenging} = [(\text{A control} - \text{A sample})/\text{A blank}] \times 100$$

where A control is the absorbance of the control reaction (containing all reagents except the test compound) and A sample is the absorbance of the test compound. Tests were carried at in triplicate.

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Appendix. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.08.010.

References

[1] A. Rivkin, Y.S. Cho, A.E. Gabarda, F. Yoshimura, S.J. Danishefsky, J. Nat. Prod. 67 (2004) 139–143.
[2] T. Ganesh, J.K. Schilling, R.K. Palakodety, R. Ravindra, N. Shanker, S. Bane, D.G.I. Kingston, Tetrahedron 59 (2003) 9979–9984.
[3] P.V. Plazzi, F. Bordi, M. Mor, C. Silva, G. Morini, A. Caretta, E. Barocelli, T. Vitali, Eur. J. Med. Chem. 30 (1995) 881–889.
[4] N. Bai, Y. Sha, Ge. Meng, Molecules 13 (2008) 943–947.
[5] D.J. Hu, S.F. Liu, T.H. Huang, H.Y. Tu, A.D. Zhang, Molecules 14 (2009) 1288–1303.
[6] K. Taori, V.J. Paul, H. Luesch, J. Am. Chem. Soc. 130 (2008) 1806–1807.
[7] A.T. Fuller, Nature 175 (1955) 722.
[8] F. Sasse, H. Steinmetz, G. Hôfle, H. Reichenbach, J. Antibiot. 56 (2003) 520–525.
[9] S. Kehraus, G.M. Konig, A.D. Wright, J. Org. Chem. 67 (2002) 4989–4992.
[10] K. Gerth, N. Bedorf, G. Hofle, H. Irschik, H. Reichenbach, J. Antibiot. 49 (1996) 560–563.
[11] H. Umezawa, K. Maeda, T. Takeuchi, Y. Okami, J. Antibiot. 19 (1966) 200–209.
[12] B. Silakowski, H.U. Schairer, H. Ehret, B. Kunze, S. Weinig, G. Nordsiek, P. Brandt, H. Blocker, G. Hofle, S. Beyer, R. Muller, J. Biol. Chem. 274 (1999) 37391–37399.
[13] H. Abe, T. Takaishi, T. Okuda, K. Aoe, T. Date, Tetrahedron Lett. 19 (1978) 2791–2794.
[14] M.F. Earle, R.I. Glazer, Cancer Res. 43 (1983) 133–137.
[15] D.N. Carney, G.S. Ahluwalia, H.N. Jayaram, D.A. Cooney, D.G. Johns, J. Clin. Invest. 75 (1985) 175.
[16] G.J. Tricot, H.N. Jayaram, C.R. Nichols, K. Pennington, E. Lapis, G. Weber, R. Hoffman, Cancer Res. 47 (1997) 4988–4991.
[17] G. Weber, U.S. Pat. 5, 405 (1995) 837.
[18] K.D. Shin, M.-Y. Lee, D.-S. Shin, S. Lee, K.-H. Son, S. Koh, Y.-K. Paik, B.-M. Kwon, D.C. Han, J. Biol. Chem. 280 (2005) 41439–41448.
[19] F.A.K. Amer, M. Hammouda, A.A.S. El-Ahl, B.F. Abdel-Wahab, J. Chin. Chem. Soc. 54 (2007) 1543–1552.
[20] A.O. Abdolhamid, A.H. El-Ghandour, A.A.M. El-Reedy, J. Chin. Chem. Soc. 55 (2008) 406–413.
[21] M. Sechi, L. Sannia, F. Carta, M. Palomba, R. Dallocchio, A. Dessi, M. Derudas, Z. Zawahir, N. Neamati, Antivir. Chem. Chemother. 16 (2005) 41–61.
[22] S. Rapposelli, A. Lapucci, F. Minutolo, E. Orlandini, G. Ortore, M. Pinza, A. Balsamo, Farmaco 59 (2004) 25–31.
[23] B. Cottineau, P. Toto, C. Marot, A. Pipaud, J. Chenault, Bioorg. Med. Chem. Lett. 12 (2002) 2105–2108.
[24] P. Cali, L. Naerum, S. Mukhija, A. Hjelmencrantz, Bioorg. Med. Chem. Lett. 14 (2004) 5997–6000.
[25] S. Shinde, W. Jadhav, R. Pawar, S. Bhusare, J. Chin. Chem. Soc. 51 (2004) 775–778.
[26] F. Al-Omran, A.A. El-Khair, J. Heterocycl. Chem. 41 (2004) 327–333.
[27] T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang, P.C. Isakson, J. Med. Chem. 40 (1997) 1347–1365.
[28] X. Deng, N.S. Mani, Org. Lett. 10 (2008) 1307–1310.
[29] A.R. Katritzky, M. Wang, S. Zhang, M.V. Voronkov, J. Org. Chem. 66 (2001) 6787–6791.
[30] J. Elguero, in: A.R. Katritzky, C.W. Rees, EF.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, vol. 3, Pergamon, Oxford, 1996, pp. 1–75.
[31] X. Deng, N.S. Mani, Org. Lett. 8 (2006) 3505–3508.
[32] T. Ichiba, W.Y. Yoshida, P.J. Scheuer, T. Higa, D.G. Gravalos, J. Am. Chem. Soc. 113 (1991) 3173–3174.
[33] D. Bhaskar Reddy, M. Muralidhar Reddy, G.V. Subbaraju, Indian J. Chem. 34B (1995) 816–822.
[34] M. Burits, F. Bucar, Phytother Res. 14 (2000) 323–328.
[35] M. Cuendet, K. Hostettmann, O. Potterat, Helv. Chim. Acta 80 (1997) 1144–1152.
[36] L.C. Green, D.A. Wagner, J. Glogowski, P.L. Skipper, J.K.S.R. Wishnok, Anal. Biochem. 126 (1982) 131–136.
[37] L. Marcocci, J.J. Maguire, M.T. Droy-Lefaix, L. Packer, Biochem. Biophys. Res. Commun. 201 (1994) 748–755.
[38] R.J. Ruch, S.J. Cheng, J.E. Klaunig, Carcinogenesis 10 (1989) 1003–1008.