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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL ISOXAZOLE DERIVED QUINOLINES

S. B. Ghodile[1]*, P. T. Kosankar[2], R. D. Raut[3]

[1]Datta Meghe Institute of Engineering, Technology and Research Sawangi (Meghe), Wardha India.
[2]Yashwantrao Chavan College of Engineering, Nagpur, India.
[3]Jankidevi Bajaj College of Science, Wardha, India.

***Corresponding Author: S. B. Ghodile**
Datta Meghe Institute of Engineering, Technology and Research Sawangi (Meghe), Wardha India.

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ABSTRACT

A series of diversely substituted Isoxazole derived quinoline (4a-g) were obtained by the reaction of various chalcones (3a-g) with hydroxylamine hydrochloride and sodium acetate in ethanol. New compounds were characterized by FT-IR, ^{1}H- NMR and Elemental analysis. Antibacterial and antifungal activities of those compounds were determined by disc diffusion method against *A. niger, A. flavus* (fungal strains), *E. coli and P. aeruginosa* (Gram negative bacteria), *S. aureus and S. pyogenes* (Gram positive bacteria) using Nystatin (for fungi) and Ciprofloxacin (for bacteria) as a standard drugs. The in vitro antifungal and antibacterial screening of the isoxazole derived quinoline (4a-g) revealed that most of the compounds in the series showed potent activity.

Key Words: Isoxazole, Quinoline, Antibacterial activity, Antifungal activity.

INTRODUCTION

Heterocyclic chemistry is a branch which is inseparable from mankind because human are totally dependent on the drugs derives from heterocyclic rings. Much attention has paid to the synthesis of nitrogen containing heterocyclic compounds like isoxazole mainly due to their broad spectrum of biological and pharmacological activities. Nitrogen containing heterocycles with an oxygen atom are considered as an important class of compounds in medicinal chemistry because of their diversified biological applications. The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Isoxazoles have illustrious history; their chemistry is associated with Ludwig Claisen, who first recognized the cyclic structure of 3-methyl-5-phenylisoxazole in 1888 and was shown to possess typical properties of an aromatic system under certain reaction conditions; particularly in basic media, it is very highly labile. Dunstan and Dymond were the first to synthesize the isoxazole ring.[1] They isolated a liquid base by heating nitroethane with aqueous alkalies to obtain 3, 4, 5-trimethylisoxazole. A very significant contribution to the development of isoxazole chemistry came between 1930– 1946 from Quilico's studies on the synthesis of ring system from nitrile oxides and unsaturated compounds.[2] Derivatives of Isoxazole[3-5] have played a crucial role in the history of heterocyclic chemistry and been used extensively important pharmacophores and synthons in the field of organic chemistry. Owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on these nuclei. Isoxazole derivatives exhibit various biological activities such as, Antibacterial,[6-8] Anticonvulsant,[9-10] Anticholestermic,[11] Anticancer,[12] Anthelmintics,[13] Antiinflammatory,[14-17] Adenosine antagonist,[18] Fungicidal,[19-21] Herbicidal,[22-23] Hypoglycemi c,[24] Muscle relaxant,[25-26] Nematocidal,[27] Insecticidal,[28] Antiviral[29] and Antimicrobial.[30] Isoxazoles are also valuable building blocks for organic synthesis since they are not only converted into important synthetic units such as β-hydroxyketones, γ-aminoalcohols, α, β-unsaturated oximes, β-hydroxynitriles and aziridine esters,[31] but also used in the synthesis of many natural products[32] Isoxazoles are generally prepared by (i) the reaction of 1, 3-diketones with hydroxylamines,[33] (ii) 1, 3-dipolar cycloaddition of nitrile oxides with alkynes,[34] and (iii) the reaction of α,β-unsaturated aldehydes and ketones with hydroxylamines.[35]

MATERIALS AND METHODS

2.1 General

Reagent and solvents were purchased from commercial sources and used without further purification unless otherwise specified. All melting points were taken using open glass capillaries and were found uncorrected. Reactions were monitored by thin- layer chromatography

carried out on 0.15-0.20mm silica gel 60F254 aluminum plates (MERCK company) using UV light as visualizing agent. The IR spectra in KBr were recorded on Perkin Elmer spectrophotometer and ^{1}HNMR spectra were recorded in DMSO on Varian Inova 300 FT MHz spectrophotometer (δ ppm) using TMS as internal standard (δ ppm). Elemental Analysis was carried out using Perkin-Elmer 240 CHN elemental analyzer.

General procedure for synthesis of novel series of differently substituted Isoxazole derived quinolines (4a-g)

Step 1: Chalcones by reaction of aldehyde with variously substituted acetophenone (Claisen-Schimidt condensation)

Equimolar quantities of substituted 2-hydroxyacetophenone 1a-g (0.01 mol) and 2-choloro-8-methylquinolone-3-carbaldehyde 2 (0.01 mol) were dissolved in ethanol (15 ml), under stirring and aqueous KOH (50%, 10 mL) was added drop wise. The reaction mixture was stirred at room temperature and kept for 14-16 hours. The reaction mixture was diluted with water and acidified with 10% HCl. The separated solid was filtered and crystallized using acetic acid to give compounds 3a-g. (Scheme 1)

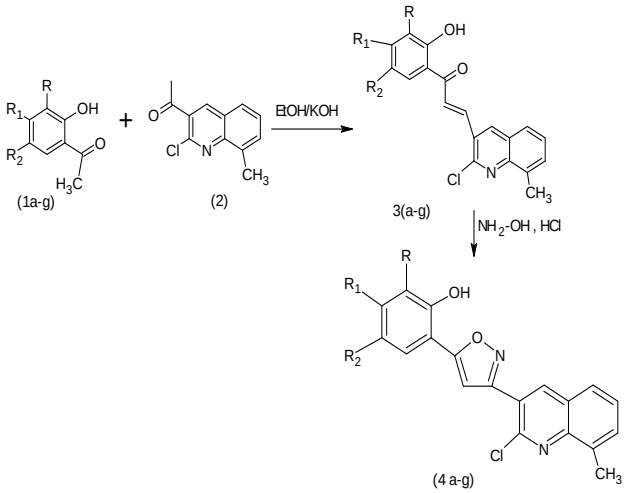
Step 2: Various Isoxazoles from Chalcones

Chalcone 0.02 mol, Hydroxylamine hydrochloride 0.02 mol and sodium acetate in ethanol 25 ml was refluxed for 6 hr. The mixture was concentrated by distilling out the solvent and poured into ice water. The precipitate obtained was filtered, washed and recrystallized (Scheme 1).

Microbiology

In vitro antibacterial and antifungal activity

The test compounds 4a-g, in measured quantities, was dissolved in Dimethyl Sulphoxide (DMSO) in a final concentration of 50µg/mL. The synthesized compounds were evaluated for antibacterial and antifungal activity by disc diffusion method (Biljana et al, 2010) against *A. niger*, *A. Flavus* (fungal strains), *E. coli* and *P. Aeruginosa* (Gram negative bacteria), *S. aureus* and *S. Pyogenes* (Gram positive bacteria) using Nystatin (for fungi) and Ciprofloxacin (for bacteria) as a standard drugs. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi and nutrient agar for bacteria medium. The filter paper disks prepared by only DMSO (as negative control) and with solution of 50 µg/L concentrations of test compounds 4a-g as well as standard compounds (Ciprofloxacin and Nystatin as positive control) were carefully placed over the spread cultures and incubated at 37 ºC for 24 h for bacteria and 28-30 ºC for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter of zones of inhibition was measured including the diameter of disk also. All determinations were made in triplicate for each of the compounds and the average value was taken.



Scheme 1: Synthesis of Isoxazole derived quinolone.

RESULT AND DISCUSSION

Compound characterization

(2Z)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2,4-dihydroxy-3,5-diiodophenyl)prop-2-en-1-one (3a):

m.p. 185 °C. IR (KBr) cm-1: 3393 (-OH), 1635 (C=O), 1574, 1485 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 9.54 (s, 1H), 8.47 (d, J= 1.6 Hz, 1H), 8.08 (d, J= 15.1 Hz, 1H), 7.93 (s, 1H), 7.87-7.73 (m, 2H), 7.62 (t, J= 7.5 Hz, 1H), 7.42 (d, J= 15.1 Hz, 1H).

(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2-hydroxy-3-iodo-5-methylphenyl) prop-2-en-1-one (3b):

m.p. 173 °C. IR (KBr) cm-1:3066(-OH), 1632 (C=O), 1569, 1487 (ring C=C), 1HNMR (300 MHz, DMSO-d6): δ 8.52 (d, J= 1.5 Hz. 1H), 8.11 (d, J= 15.1 Hz, 1H), 7.89-7.73 (m, 4H), 7.68-7.55 (m, 2H), 7.46 (d, J= 15.1 Hz, 1H), 2.30 (d, J= 1.0 Hz, 4H).

(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2-hydroxy-3, 5-diiodophenyl)prop-2-en-1-one(3c):

m.p. 148°C. IR (KBr) cm-1: 2995(-OH), 1635(C=O), 1569, 1492 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48(d, J= 1.6 Hz, 1H), 8.24 (dd, J= 11.5, 1.5 Hz, 3H), 8.10 (d, J= 15.1 Hz, 1H), 7.88-7.73 (m, 3H), 7.62(t, J= 7.5 Hz, 1H), 7.44 (d, J= 15.1 Hz, 1H).

(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(3,5-dichloro-2,4-dihydroxyphenyl) prop-2-en-1-one(3d):

m.p. 156°C. IR (KBr) cm-1: 3405 (-OH), 1635 (C=O), 1575, 1485 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.47 (d, J= 1.6 Hz, 1H), 8.10 (d, J= 15.1 Hz, 2H), 7.87-7.73 (m, 3H), 7.68-7.55 (m, 3H), 7.47 (d, J= 15.0 Hz, 1H).

(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(3,5-dibromo-2,4dihydroxyphenyl) prop -2-en-1-one(3e):

m.p. 179°C. IR (KBr) cm-1: 3396 (-OH), 1637(C=O), 1570, 1480 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.47 (d,J= 1.6 Hz, 1H), 8.09 (d, J= 15.1 Hz, 2H), 7.87-

7.72 (m, 4H), 7.62 (t, J= 7.5 Hz, 1H), 7.45 (d, J= 15.1 Hz, 2H).

(2E)-1-(5-chloro-2-hydroxy-3-iodophenyl)-3-(2-chloro-8-methylquinolin-3-yl)prop-2-en-1-one(3f):
m.p. 162°C. IR (KBr) cm-1: 3032(-OH), 1630(C=O), 1569, 1496(ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48 (d, J= 1.6 Hz, 1H), 8.17-8.00 (m, 4H), 7.88-7.73 (m, 3H), 7.62 (t, J= 7.5 Hz. 1H), 7.46 (d, J= 15.1 Hz, 1H).

(2E)-1-(3-bromo-5-chloro-2-hydroxyphenyl)-3-(2-chloro-8-methylquinolin-3-yl) prop-2-en-1-one (3g):
m.p. 160°C. IR (KBr) cm-1: 3078 (-OH), 1637 (C=O), 1571, 1490 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48 (d,J=1.5 Hz, 1H), 8.18-8.01(m, 3H), 7.88-7.73 (m,4H), 7.62 (t, J= 7.5 Hz, 1H), 7.47 (d, J= 15.1 Hz, 1H).

4-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl]-2, 6-diiodobenzene-1,3-diol (4a):
m.p. 185 °C. IR (KBr) cm-1: 1640.5 (C=C), 1370.6 (C-N), 1672.6 (C=N), 3100.8 (C-H, broad), 1475.6, 1610.6 (C=C, narrow, aromatic ring), 3400.7 (Ar-OH, broad), 1234.7 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.68 (t, J= 7.4 Hz, 1H), 7.84 (dd, J= 7.5 Hz, 1H), 7.57 (dt, J= 7.5 Hz, 1H), 8.43 (d, J= 1.5, 1H), 7.40 (d, 2H), 9.54 (s, 2H), 2.6 (s, 3H).

2-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl]-6-iodo-4-methylphenol (4b):
m.p. 185 °C. IR (KBr) cm-1: 16407.6 (C=C), 1390.7 (C-N), 1660.8 (C=N), 3106.5 (C-H, broad), 1463.8, 1617.6 (C=C, narrow, aromatic ring), 3410.6 (Ar-OH, broad), 1245.8 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.70- 7.51 (m, 4H), 7.84 (dd, J= 7.3, 1.8 Hz, 1H), 7.76-7.64 (m, 2H), 8.45 (d, J= 1.5, 1H), 9.54 (s, 1H), 2.6 (s, 3H).

2-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl]-4, 6-diiodophenol (4c):
m.p. 185 °C. IR (KBr) cm-1: 1630.8 (C=C), 1310.2 (C-N), 1668.6 (C=N), 3090.7 (C-H, broad), 1480.3, 1610.8 (C=C, narrow, aromatic ring), 3415.4 (Ar-OH, broad), 1250.6 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.78-7.62 (m, 2H), 7.84 (dd, J= 7.4, 1.6 Hz, 1H), 7.57 (dt, J= 7.5, 1.5, 1H), 8.43 (d, J= 1.6, 1H), 8.03 (d, J= 1.6, 1H), 9.54 (s, 1H), 2.6 (s, 3H), 8.13 (d, J= 1.5, 1H).

2,4-dichloro-6-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl] benzene-1,3-diol(4d):
m.p. 185 °C. IR (KBr) cm-1: 1637.6 (C=C), 1330.4 (C-N), 1668.3 (C=N), 3010.6 (C-H, broad), 1455.6, 1608.8 (C=C, narrow, aromatic ring), 3420.8 (Ar-OH, broad), 1230.9 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.68 (t, J= 7.4, 1H), 7.84 (dd, J= 7.5, 1.6 Hz, 1H), 7.56 (dt, J= 7.5, 1.5, 1H), 8.43 (d, J= 1.6, 1H), 6.99 (s, 2H), 7.42 (s, 2H), 2.6 (s, 3H).

2,4-dibromo-6-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl] benzene-1,3-diol(4e):
m.p. 185 °C. IR (KBr) cm-1: 1625.8 (C=C), 1338.9 (C-N), 1650.8 (C=N), 3090.3 (C-H, broad), 1445.1, 1620.3 (C=C, narrow, aromatic ring), 3418.2 (Ar-OH, broad), 1210.7 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.68 (t, J= 7.4, 1H), 7.84 (dd, J= 7.5, 1.6 Hz, 1H), 7.57 (dt, J= 7.5, 1.5, 1H), 8.43 (d, J= 1.6, 1H), 7.03 (s, 2H), 7.42 (s, 2H), 2.6 (s, 3H).

4-chloro-2-[3-(2-chloro-8-methylquinolin-3-yl)-1,2-oxazol-5-yl]-6-iodophenol (4f):
m.p. 185 °C. IR (KBr) cm-1: 1620.3 (C=C), 1315.2 (C-N), 1629.8 (C=N), 3060.1 (C-H, broad), 1440.5, 1603.8 (C=C, narrow, aromatic ring), 3430.6 (Ar-OH, broad), 1205.2 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.84 (dd, J= 7.4, 1.6 1H), 7.57 (dt, J= 7.5, 1.5 Hz, 1H), 8.43 (d, J= 1.6, 1H), 7.74- 7.62 (m, 2H), 7.77 (s, 1H), 2.6 (s, 3H), 9.54 (s, 1H), 7.92 (d, J= 1.5, 1H)

2-bromo-4-chloro-6-[3-(2-chloro-8-methylquinolin-3-yl) isoxazol-5-yl]phenol(4g):
m.p. 185 °C. IR (KBr) cm-1: 1645.6 (C=C), 1316.1 (C-N), 1657.6 (C=N), 3073.6 (C-H, broad), 1438.2, 1638.3 (C=C, narrow, aromatic ring), 3408.9 (Ar-OH, broad), 1233.6 (C-O-C). 1HNMR (300 MHz, DMSO-d6): δ 7.75- 7.62 (m, 4H), 7.84 (dd, J= 7.4, 1.6 Hz, 1H), 7.57 (dt, J= 7.4, 1.5, 1H), 8.43 (d, J= 1.6 1H), 2.6 (s, 3H), 7.79 (s, 1H)

Table 1: Physical and analytical data of the newly synthesized compounds 3a-g.

Compound	R	R_1	R_2	Mol. Formula	Yield (%)	Elemental analysis% found(calculated)		
						C	H	N
3a	I	OH	I	$C_{19}H_{12}ClI_2NO_3$	72	38.59 (38.54)	2.0 (2.02)	2.28 (2.36)
3b	I	H	CH_3	$C_{20}H_{15}ClINO_2$	70	51.71 (51.75)	3.19 (3.23)	3.08 (3.01)
3c	I	H	I	$C_{19}H_{12}ClI_2NO_2$	75	39.66 (39.61)	2.04 (2.08)	2.40 (2.43)
3d	Cl	OH	Cl	$C_{19}H_{12}Cl_3NO_3$	70	55.71 (55.79)	2.95 (2.93)	3.46 (3.42)
3e	Br	OH	Br	$C_{19}H_{12}Br_2ClNO_3$	73	45.80 (45.82)	2.38 (2.41)	2.86 (2.81)
3f	I	H	Cl	$C_{19}H_{12}Cl_2INO_2$	68	47.13 (47.09)	2.43 (2.47)	2.93 (2.89)
3g	Br	H	Cl	$C_{19}H_{12}BrCl_2NO_2$	71	52.12 (52.16)	2.76 (2.74)	3.25 (3.20)

Table 2: Physical and analytical data of the newly synthesized compounds 4a-g.

Compounds	R	R_1	R_2	Mol. Formula	Yield (%)	Elemental analysis% found(calculated)		
						C	H	N
4a	I	OH	I	$C_{19}H_{11}ClI_2N_2O_3$	65	37.39 (37.75)	1.76 (1.83)	4.02 (4.13)
4b	I	H	CH_3	$C_{20}H_{14}ClIN_2O_2$	68	50.16 (50.39)	2.86 (2.96)	5.62 (5.88)
4c	I	H	I	$C_{19}H_{11}ClI_2N_2O2$	66	38.55 (38.77)	1.48 (1.88)	4.60 (4.76)
4d	Cl	OH	Cl	$C_{19}H_{11}Cl_3N_2O_3$	64	53.98 (54.12)	2.42 (2.63)	6.38 (6.64)
4e	Br	OH	Br	$C_{19}H_{11}Br_2ClN_2O_3$	62	44.38 (44.70)	2.08 (2.17)	5.11 (5.49)
4f	I	H	Cl	$C_{19}H_{12}Cl_2IN_3O$	69	45.58 (45.91)	2.16 (2.23)	5.17 (5.64)
4g	Br	H	Cl	$C_{19}H_{12}BrCl_2N_3O$	64	50.19 (50.70)	2.32 (2.46)	6.20 (6.22)

Biological activity

Newly synthesized isoxazole derived quinoline 4a-g exhibited a varying pattern of antibacterial and antifungal activities; the results are tabulated in Table 3. In case of *E. coli*, compound 4c displayed equipotent activity, compound 4e showed moderate activity while compounds 4a and 4g showed good activity. Compound 4b showed moderate activity and compounds 4a, 4c exhibits good against *P. aeruginosa*. In case of S. *aureus*, compound 4c showed equipotent activity with respect to ciprofloxacin and compound 4b, 4f found to be moderately active. Compound 4f showed equipotent activity while compounds 4c, 4d exhibited good activity against *S. pyogenes.*

Some of the compounds showed a significant level of activity in comparison with standard antifungal dgrug (Nystatin, 50µg/L concentration). Compounds 4a and 4g showed moderate activity, compound 4d, and 4e showed good activity against *A. niger*. In case of *C. albicans*, compound 4b and 4g showed moderate activity while compounds 4a and 4d displayed good inhibitory activity. The preliminary in vitro antifungal and antibacterial screening of the compounds 4a-g revealed that some of the compounds showed potent activity. Therefore, the present study is valuable for finding the new drugs against bacterial and fungal diseases.

Table 3: Results of Antibacterial and antifungal activity of newly synthesized compounds 4a-g.

Compounds	Gram Negative bacteria		Gram Positive Bacteria		Fungi	
	E. coli	P. aeruginosa	S. aureus	S. pyogenes	A. niger	C. albicans
	Zone of Inhibition (mm)					
4a	23	24	21	21	26	26
4b	22	25	22	22	24	28
4c	25	24	23	24	23	24
4d	21	22	19	24	25	26
4e	24	21	20	21	25	25
4f	21	21	22	25	23	23
4g	23	22	21	22	27	27
ciprofloxacin	25	26	23	25	-	-
Nystatin	-	-	-	-	28	29

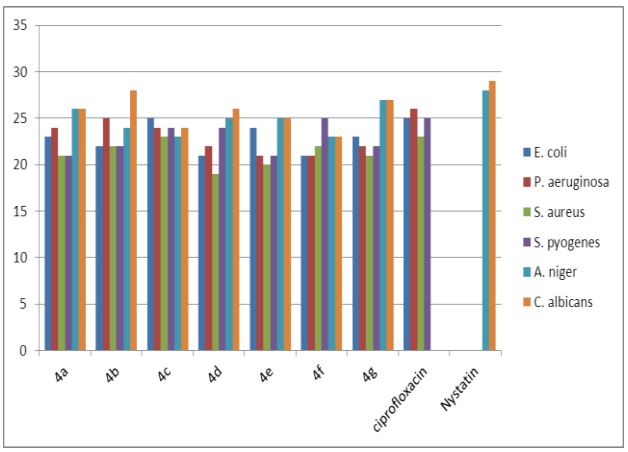


Figure 1: Graphical representation of antibacterial and antifungal activity of isoxazole derived quinolines (4a-g).

CONCLUSION

Newly synthesized isoxazole derived quinolines is found to have significant antibacterial and antifungal activities. The antimicrobial study show that these heterocycles accommodating both subunits i.e. isoxazole and quinoline are expected to prove the therapeutic relevance and its utility in medicinal chemistry and drug development.

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REFERENCE

1. Dunstan W R and Dymond T S. The action of alkalis on the nitro-compounds of the paraffin

series. Formation of isoxazoles. J Chem Soc, 1891; 59: 410-433.
2. a) Quilico A, Stagno d'Alcontres G and Grunanger P. A New Reaction of Ethylenic Double Bonds. Nature. 1950; 166: 226-227. b) Quilico A, Gazz MF. Chim Ital, 1930; 60: 172.
3. PMG Swamy; YS Agasimundin, Rasayan J.Chem., 2008; 1: 421.
4. R Kalirajan; SU Sivakumar; S Jubie; B Suresh, International J. Chem TechResearch., 2009; 1: 27.
5. U Gupta; V Sareen; V Khatri; S Chugh, Indian J. Heterocyclic Chem., 2004; 13: 351-4.
6. B Victor; J Safir; R Sidney, Chem. Abstr., 1970; 72: 79017d.
7. G P Reddy; E Rajendra; AK Murthy, Indian J. Heterocycle., 199; 3: 233.
8. T Tochiro; K Shrji; I Shinji; M Hiroshi; S Akira; VHiroshi, Chem. Abstr., 1984; 99: 88188.
9. TU Quazi, Pak. J. Sci. Ind. Res., 1984; 27: 326.
10. R Major; B Eisele; P Mutler; H Grube, Chem. Abstr., 1988; 108: 67456r.
11. LiW T; DR Hwang; CP Chen; CW Shen; CL Huang; TW Chen; CH Lin; SJ Chen SH Wu; CT Chen, J. Med. Chem., 2003; 46: 1706.
12. S Rung; D Dus, Pharmazie, 1994; 49; 727.
13. Vamanauchi Pharm. Co. Ltd, Chem. Abstr., 1984; 100: 34538.
14. P T Gallagher; TA Hicka; GW Mullier, Chem. Abstr., 1988; 108: 6499K.
15. A Ando; RW Stevens, Chem. Abstr, 1995; 122: 56037x.
16. W Wells; A Michele; H Todd; H Dennis, Chem. Abstr., 2002; 136: 340680j.
17. I A Shehata; RA Glannoh, J. Heterocycl. Chem., 1987; 24: 1291.
18. M D Mackie; HS Anthony; WJR Howe; SP John; WS Marry,Chem. Abstr., 1994; 120: 164153z.
19. G D Diana; CP Michel, Chem. Abstr., 1983; 98: 1667.
20. M Moriyusu, H Yusui, Chem. Abstr., 1984; 99: 88188.
21. A K Banerjee; A Forsch, Chem. Abstr., 1995; 122: 160522n.
22. M Tibor; PS Neil; SP Henry, Chem. Abstr., 1994; 121: 255784t.
23. I Masatoshi; T Akie; G Kyoto, Chem. Abstr., 1996; 124: 86995s.
24. Nippon Chemiphar Co. Ltd, Chem. Abstr., 1984; 99: 17574.
25. T Taate; K Natira; H Fukhola, Chem. Pharm. Buld., 1987; 35(9): 37769.
26. D J David; DB Allon; EA Frederick, Chem. Abstr., 1978; 88: 132015k.
27. S Ozkan; D Kudir; A Okay; A Ahmet, Chem. Abstr., 1999; 131: 5221f.
28. CP Alfred; CDHerman; D Nancy; B Daniel, Chem. Abstr., 1996; 124: 3055m.
29. K Tomit; Y Takahi: H Vdaira, Ann. Sankyo Res. Lab., 197; 1: 25.
30. (a) H Schutz. Bezodiazepines. (Springer, Heidelberg), 1982(b) JK Landquist. in Comprehensive Heterocyclic Chemistry, Vol. 1, Katritzky A R & Rees C W (Pergamon, Oxford), 1984, 166-170. (c) RI Fryer. Bicyclic Diazepines, in Comprehensive Heterocyclic Chemistry edited by Taylor E C, Vol. 50, Chapter II, (Wiley, New York), 1991(d) LO Randall, B Kappel. in Benzodiazepines, edited by (Raven Press, New York), 1973; 27.
31. (a) Kozikowski, A. P.; Stein, P. D. J. Am. Chem. Soc.1982, 104, 4023. (b) Curran, D. P. J. Am. Chem. Soc. 1983, 105, 5826. (c) Kim, B. H.; Chung, Y. J.; Ryu, E. J. Tetrahedron Lett. 1993, 34, 8465. (d) Bode, J. W.; Carreira, E. M. Org. Lett. 2001, 3, 1587. (e) Kozikowski, A. P.; Chen, Y. Y. J. Org. Chem. 1981, 46, 5248. (f) Muller, I.; Jager, V. Tetrahedron Lett. 1982, 23, 4777. (g) Jager, V.; Grund, H. Angew. Chem., Int. Ed. 1976, 15, 50. (h) Lee, S. Y.; Lee, B. S.; Lee, C. W.; Oh, D. Y. J. Org. Chem. 2000, 65, 256. (i) Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. J. Org. Chem.1967, 32, 1387. (k) Yashiro, A.; Nishida, Y.; Kobayashi, K.; Ohno, M. Synlett, 2000; 361.
32. (a) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. Synthesis 1987, 857. (b) Kotyatkina, A. I.; Zhabinsky, V. N.; Khripach, V. A. Russ. Chem. Rev, 2001; 70: 641.
33. Eicher, T.; Hauptmann, S.; Speicher, A. The Chemistry ofHeterocycles: Structure, Reactions, Syntheses, and Applications;Wiley-VCH: Weinheim, 2003; 138.
34. (a) For review, see: Jager, V.; Colinas P. A. In Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; Padwa, A., Ed.; Wiley: Hoboken, NJ, 2002; 361. (b) Xu, J.; Hamme, A. T. Synlett 2008, 919. (c) L. Cecchi, F. De Sarlo, F. Machetti, Eur. J. Org. Chem. 2006, 4852. (d) T. V. Hansen, P. Wu, V. V. Fokin, J. Org. Chem, 2005; 70: 7761.
35. (a) For recent reviews, see: (a) Wakefield, B. J. In Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; Shaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 2001; 229. (b) Pinho e Melo, T. M. V. D. Curr. Org. Chem, 2005; 9: 925.