

Synthesis, characterization and biological activity studies on some disubstituted isoxazoles

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Abstract : A series of eleven 3, 5– disubstituted isoxazole derivatives have been synthesized by a four step process involving cyclization in the final step within one of the substituent. Derivatives were characterized using IR, NMR and mass spectral study. Antifungal and antibacterial studies have been performed on the derivatives and three of the derivatives have been found to show good activity.

(Keywords : disubstituted isoxazoles, antifungal, antibacterial activity, spectral studies)

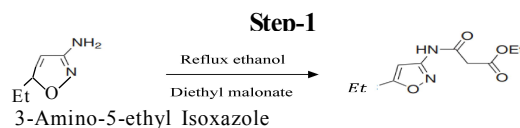
Introduction

The development of microbial drug resistance is a pervasive issue in the management of numerous infections. For medicinal chemists, finding new antibiotics for the treatment of infections remains a key issue. Because of its biological properties, which include the inhibition of HIV integrase¹, anti-inflammatory², anticancer³, antibacterial⁴, anticonvulsant⁵, analgesic, antitubercular, antifungal, and anti-allergic activities, the 1,3,4-oxadiazole moiety has emerged as a key structural motif for the development of new drugs. Raltegravir, an antiviral drug, zibotentan, an anticancer agent, fenadiazole, a hypnotic drug, nesapidil, an antihypertensive agent, and furamizole, an antibiotic are a few compounds with 1,3,4-oxadiazole derivatives that are now used as medications. As part of our on going research on physiologically active isoxazoles. Extensive studies have been carried out on mono, Di and trisubstituted isoxazole derivatives regarding synthesis, characterization

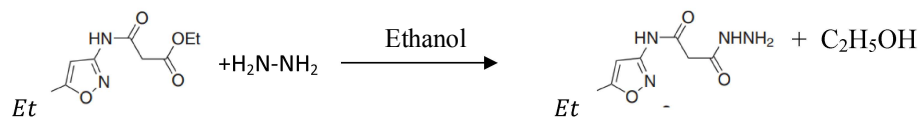
and biological evaluation [1-5]. Consequently, synthesis, characterization and biological activities study on a series of 3, 5 – disubstituted isoxazoles is being communicated in the present paper.

Experimental

Analytical data and spectral studies have been critically analyzed for the elucidation of structures. Analytical data were obtained by TLC. Spectral studies performed were IR, ¹H and ¹³CNMR. A four step microwave assisted synthetic route as depicted in the following scheme has been used. Cintex melting point apparatus was used for recording melting points. Values are uncorrected. Silica gel plates used for TLC was precoated 60F(254) which was obtained from Merck . IR spectra were recorded as KBr pellets and instrument used was Perkin Elmer BX series. Bruker spectrometer was used for recording NMR spectra. Magnetic field strengths for ¹HNMR was 400 MHz and 1000 MHz for ¹³CNMR. Solvents used were CDCl₃ or DMSO -d₆. Internal standard used was TMS. Elemental analysis was done with Carlo -Erba 106 or Perkin Elmer 240 analyzer.

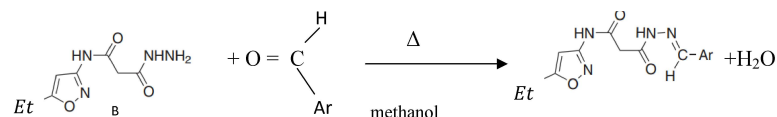


Step-II



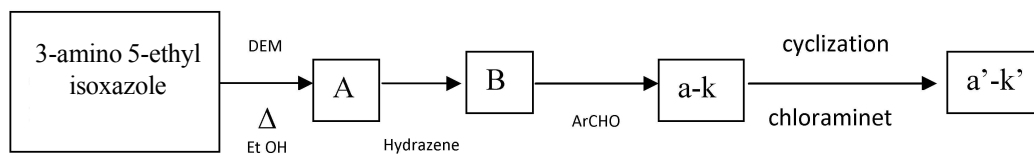
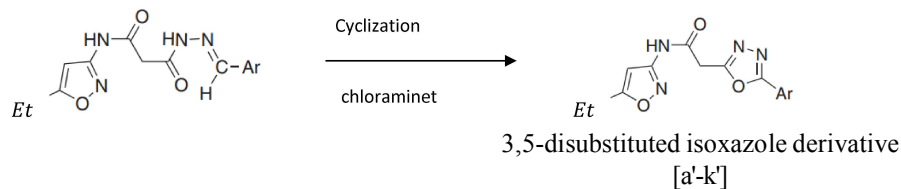
[B]

Step-III



[a-k]

Step-IV (Final Step)



Result and Discussion

Antibacterial and antifungal activity has also been studied. The data for antifungal activity is shown in Table 1. Table 2 presents data for antibacterial activity. For structural elucidation of 3, 5 - disubstituted isoxazole derivatives, analytical and spectral studies were used. Spectral studies include Infrared, NMR and ESI - MS spectra. The intermediates a - k exhibit characteristic double

signals in their ^1H NMR spectra for each of the proton around azomethinic $\text{C}=\text{N}$ bond. This aspect of spectra suggests compounds to exist in two isomeric forms E/Z. Integration values of proton signals indicate isomers to exist in the ratio 3:1.

Anti fungal Activity

Table-1
N-(5-ethylisoxazol-3-yl)-2-(5-aryl-1,3,4-oxadiazol-2-yl)acetamides

Compound concentration	<i>A. niger</i>	<i>C. tropicum</i>	<i>R. oryzae</i>	<i>F. moniliforme</i>	<i>C. lunata</i>
5a'	52.6	46.6	51.1	41.3	50.6
5b'	69.2	70.2	72.6	69.9	65.6
5c'	56.1	57.1	58.1	61.1	59.6
5d'	75.1	77.3	80.6	73.3	69.6
5e'	48.1	51.1	48.6	53.3	57.3
5f'	63.3	65.1	72.6	60.6	73.6
5g'	55.9	58.4	59.2	60.1	61.2
5h'	47.3	42.6	40.3	38.6	31.6
5i'	39.1	38.4	31.3	37.1	51.1
5j'	51.1	55.3	49.9	48.2	59.1
5k'	45.6	60.2	55.4	48.2	39.6
<i>Clotrimazole</i>	26.6	30.7	33.6	25.6	35.9

Isoxazole derivatives, a' - k', have been tested for antifungal activity against five pathogens fungi namely, *A. Niger*, *C tropicum*, *R aryaee*, *F moniliforms* and *C lunata*. Significant activity against all the five pathogens was found. The standard drug used for comparison was clotrimazole. Activity data are shown as a zone of

inhibition at 100 micrograms per mL. Highest activity are found for b' and f' which inhibit the growth to the remarkable extent. This may be due to presence of chloro, bromo and nitro substituents on the benzene ring. The remaining derivatives have moderate activity.

Anti Bacterial Activity

Table-2
N-(5-ethylisoxazol-3-yl)-2-(5-aryl-1,3,4-oxadiazol-2-yl)acetamides

Compound concentration	<i>P. aeruginosa</i>	<i>K. aerogenes</i>	<i>C. violaceum</i>	<i>B. subtilis</i>	<i>B. sphaericus</i>	<i>S. aureus</i>
5a'	21	17	19	20	16	16
5b'	10	10	7	10	7	8
5c'	17	16	14	17	17	15
5d'	11	8	8	7	7	7
5e'	11	15	16	16	13	15
5f'	13	11	15	12	12	11
5g'	19	14	17	17	16	14
5h'	18	15	21	18	19	20
5i'	20	17	22	20	18	17
5j'	20	30	19	21	17	14
5k'	24	24	20	19	18	15
<i>Ciprofloxacin</i>	29	24	25	21	21	24

3, 5-disubstituted isoxazole derivatives a'-k' show good antibacterial activity when compared with the activity of standard drug ciprofloxacin. Excellent MIC values have been observed for the isoxazole derivatives b' and k'. Compound d' have exceptional activity which may be attributed to

the presence of nitro group on the phenyl ring. Moderate activity has been shown by the remaining derivatives a', c', e', f', g', h', l' and j'. Degree of inhibition has been found to depend on test compound and bacteria .

Reference

1. C. W. Moth, J.J. Prusakiewicz, L.J. Marnett, T. Lybrand, P. Stereo selective binding of indomethacin ethanolamide derivatives to cyclooxygenase-1. *J. Med. Chem.*, **48**, 3613 (2005).
2. X. J. Zou, L. H. Lai, G.Y. Jin, Z. X. Zhang Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J. Agric. Food Chem.*, **50**, 3757 (2002)
3. G.D. Reddy, S. Park, H. M. Cho, T.J. Kim, M.E. Lee, Antiallergic activity profile in vitro RBL-2H3 and in vivo passive cutaneous anaphylaxis mouse model of new sila-substituted 1,3,4-oxadiazoles. *J. Med. Chem.*, **55**, 6438 (2012)
4. A. Savarino, A historical sketch of the discovery and development of HIV-1 integrase inhibitors. *Expert Opin. Investig. Drugs*, **15**, 1507 (2006).
5. N.D. James, J.W. Growcott, *Zibotentan. Drugs Future.*, **34**, 624 (2009).
6. K. Hirpara, S. Patel, A. Joshi, H. Parekh, Synthesis and biological evaluation of some cyanopyridines and isoxazoles. *Indian J. Heterocycl. Chem.*, **13**, 221 (2004)
7. Li, W.-T.; Hwang, D.-R.; Chen, C.-P.; Shen, C.-W.; Huang, C.-L.; Chen, T.-W.; Lin, C.-H.; Chang, Y.-L.; Chang, Y.-Y.; Lo, Y.-K. et al. Synthesis and biological evaluation of N-heterocyclic indolylglyoxylamides as orally active anticancer agents. *J. Med. Chem.*, **46**, 1706 (2019)
8. N.G. Miranada, M. B.E. Leanos, P.M. Vilchis, S. F. Solorzano, In vitro activity effects of combinations of cephalothin, dicloxacillin, imipenem, vancomycin and amikacin against methicillin-resistant *Staphylococcus* spp. *Strains Ann. Clin. Microbial Antimicrob.*, **5**, 25 (2006).
9. M.M. Thakkar, S. Winston, R.W. McCarley, Effect of microdialysis perfusion of 4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3-ol in the perifornical hypothalamus on sleep-wakefulness: role of subunit containing extrasynaptic GABA receptors. *Neuroscience*, **153**, 551 (2008).
10. K. Ramu, M. Srinivas, M.P.S. Murali Krishna, M. P. S.; M. Parusharamulu, Y.N. Reddy, Synthesis and biological evaluation of 3,4-dihydro-3-(3-methylisoxazol-5-yl)-2H-benzo[e][1,3]oxazine derivatives as anticancer agents. *Lett. Org. Chem.*, **15**, 124 (2018).
11. E. Rajanarendar, K. Ramu, Shiva Rami Reddy, A.; Shaik, F. P. Synthesis and in vitro study of novel isoxazolybenzamides, acrylamides and propanamides as antifungal agents. *Indian J. Chem.*, **47B**, 1284 (2008)
12. E. Rajanarendar, K. Ramu, D. Karunakar, P. Ramesh, Microwave-assisted synthesis of new isoxazolytriazinethiones and isoxazolyloxadiazinethiones in dry media. *J. Heterocycl. Chem.*, **42**, 711 (2005)