Research Article

Synthesis and Screening of some Novel 2,5 Substituted (1,3,4) Oxadiazol containing Indole Moiety

S. Muralikrishna*, P. Raveendra Reddy, L. K. Ravindranath and P. Jagadeeswara rao

Department of Chemistry, S. K. University, Anantapur - 515003,A. P. India

Abstract

A series of some novel 2-[5-(substituted phenyl)-[1,3,4]oxadiazol containing indole moiety were synthesized byusing of indole with mannich base on reaction to give 3-(piperazin-1-yl)methyl)-1H-indol**(3**) which is turned into Ethyl 2-(3-piperazin-1-yl)methyl)-1H-indol-1-yl)acetate**(4)**.The compound**(4)** on reaction with hydrazinehydrate in ethanol solvent under reflux. The subsequent treatment of 2-(3-((piperazin-1-yl)methyl)-1H-indol-1-yl)acetohydrazide**(5)**, with an appropriate aromatic carboxylic acid in presence of polyphosparic acid under reflux afforded the title compounds. The chemical structures of the newly synthesized compounds were elucidated by their IR, ^{1}H NMR and Mass spectral data analysis. Further the compounds are used to find out their ability towards anti microbial and nematicidal activity.

Keywords: Antibacterial activity, Antifungal activity, Indole, PPA, mannich base, 1,3,4-oxadiazole

***Correspondence**
S. Muralikrishna,
Email: muralisphd@gmail.com

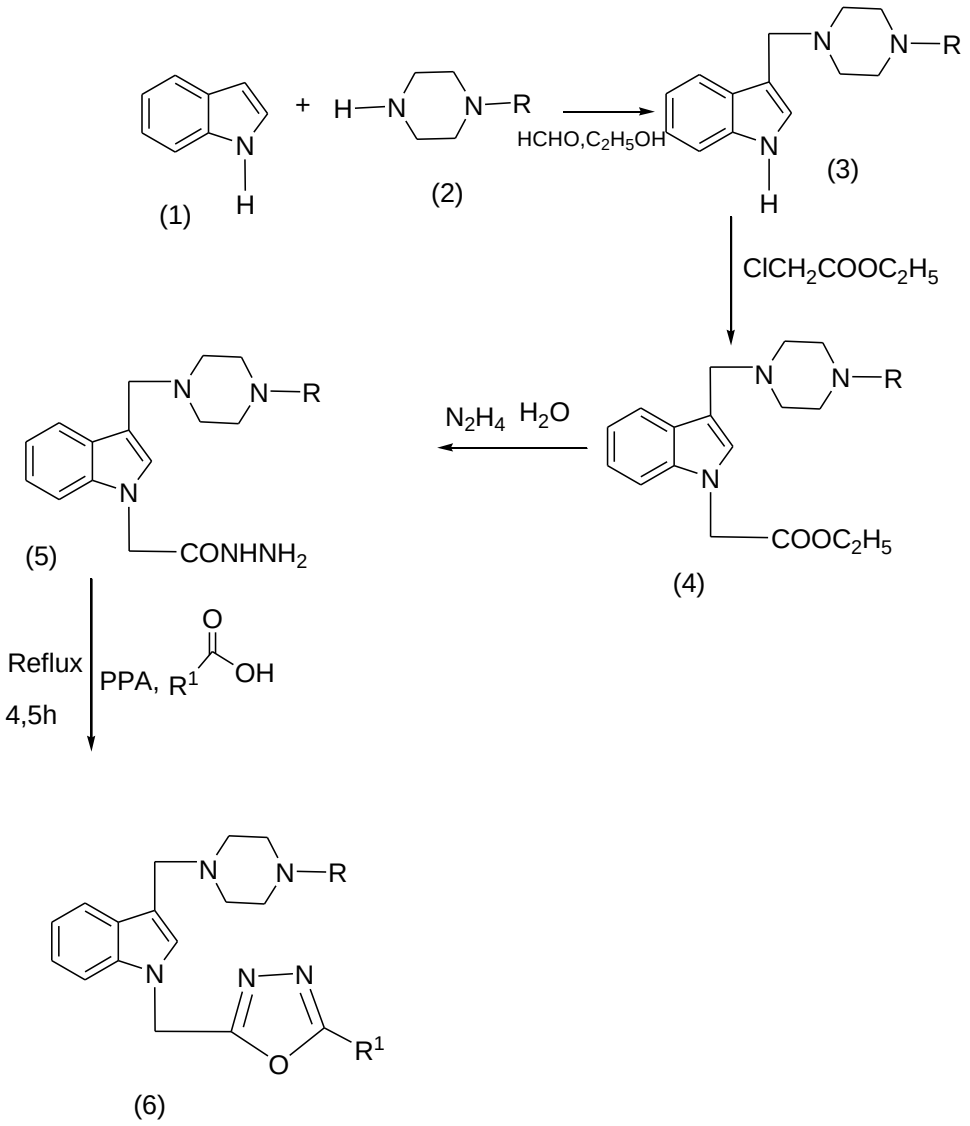
Introduction

Recent drug discovery studies have focused on the design and synthesis of small molecules that have an indole nucleus as the core structure and that act as tubulin inhibitors. [1] Drugs that bind to tubulin act by interfering with the mitosis of cells during the M-phase, resulting in mitotic arrest and eventually leading to apoptosis. [2] Therefore, microtubules are a sensitive target for the development of anticancer drugs. Due to the introduction of vinca alkaloids such as vincristine and vinblastine for the clinical therapy of cancer, indole carrying compounds have generated considerable interest[3−8]. A large number of synthetic indole-containing drugs and clinical candidates have been identified over the past few years

Chang and co-workers reported a large number of compounds with indole core structure. In addition to the synthesis and evaluation of the anticancer activity of these compounds, they have revealed some SAR and pharmacophore modeling data. [4,5,9−13] Research on 1- and 3-aroylindoles[9] showed that 3-substituted indole derivatives exhibited significant activity compared with 1-aroylindoles and the electronic effects on the indole ring were important for activity potency.[11]

The oxadiazole chemistry has been developed extensively and is still developing. Presently there are a number of drugs used clinically, which comprise oxadiazole moiety in association with various heterocyclic rings. 1, 3,4-oxadiazoles are biologically active, synthetically useful and important heterocyclic compounds. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades for biological, medicinal and agricultural reasons. Different classes of oxadiazole compounds possess an extensive spectrum of pharmacological activities. Differently substituted oxadiazole moiety has also been found to have other important activities such as antibacterial,[12] antimalarial,[13] anti-inflammatory,[14] antifungal,[15]anticonvulsant,[16] analgesic,[17] antimicrobial,[18] antimycobacterial,[19] anticonvulsant,[20] antitumor,[21]

antimalarial,[22]herbicidal,[23] vasodialatory,[24] cytotoxic,[25] hypolipidemic,[26]ulcerogenic[27] and antiedema.[28] The biological significance of these compounds impelled us to continue the work on the synthesis of some new and novel heterocycles.



R	H	H	H	H	H	H
R^1	C_6H_5	$C_6H_4CH_3$	$C_6H_4C_2H_5$	C_6H_4Cl	C_6H_4Br	$C_6H_4NO_2$

Results and Discussion

The synthesis of indole derivatives, indole containing active hydrogens linked with 1,3,4 oxadiazole derivatives 6(a-f) was accomplished in a two stage process. In the first stage indole treated with secondary amine and mannich bases formation 3-(piperazin-1-yl)methyl)-1H-indol**(3)**. For the formation of hetero cyclic compounds ,acid hydrazide can be considered as a useful intermediate hence the treatment of Ethyl 2-(3-piperazin-1-yl)methyl)-1H-indol-1-

yl)acetate**(4)** with hydrogen hydrate to afford the corresponding 2-(3-((piperazin-1-yl)methyl)-1H-indol-1-yl)acetohydrazide**(5)** and finally **(5)** is treated with poly phosphoric acid, corboxilic acid, reflux 4,5hrs to obtain 1-((phenyl (1,3,4-oxadiazol-2-yl)methyl)-3-(piperazine-1-yl)methyl)-1H-indole6(a).

The infrared spectral study for all the title compounds has been conducted to confirm the presence of functional groups assigned to them.All these compounds showed the characterstic absorption bands 1250-3050 cm^{-1}. ^{1}HNMR ^{13}CNMR spectra of these compounds 6(a-f) have been recorded and interpreted in support of the structure proposed based on their synthesis.

The synthesized compounds were evaluated for their antimicrobial activity. The screening data shown in tables 1 and 2 indicate that the compounds.

Experimental section

Chemicals and reagents used in the current study were of analytical grade. The reactions were monitored by thinlayer chromatography (TLC) on Merck pre-coated silica GF254 plates. Melting points were determined usinga Mettler Toledo FP62 capillary melting point apparatus (Mettler-Toledo, Greifensee, Switzerland) and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One series FT-IR apparatus (Version5.0.1) (Perkin Elmer, Norwalk, CT, USA), using potassium bromide pellets; the frequencies were expressedin cm^{-1}. The ^{1} H- and ^{13}C-NMR spectra were recorded with a Varian Mercury-400 FT-NMR spectrometer.

(Varian, Palo Alto, CA, USA), using tetramethylsilane as the internal reference, with chloroform-$CDCl_3$ as solvent, the chemical shifts were reported in parts per million (ppm) and coupling constants (*J*) were given in hertz (Hz). Elemental analyses were performed on a LECO 932 CHNS instrument (Leco-932, St. Joseph, MI,USA) and analyses for C, H, and N were within • } 0.4% of the theoretical values.

General procedure for the synthesis of compounds (3):

Indole (1) (2 mmol, 235 mg) was dissolved in 20 mL of ethanol-water (1:1) solution, and formaldehyde 37% (3mmol) and substituted piperazine (2) (2 mmol) were added. The mixture was stirred at room temperature and the reaction was controlled by TLC in benzene:methanol (9:1) and toluene:ethyl acetate:diethylamine (75:25:1).At the end of the reaction, the precipitate was filtrated, dried, and recrystallized using an appropriate solvent.
Yield: 45%: mp 179.7 ^{0} C. IR (KBr) √ in cm^{-1} : 3130 (N-H), 3095-2756 (C-H). 1H-NMR (CDCl3): δ 8.10 (bs,1H, indole N-H), 7.77 (d, 1H, indole H4 , *J* = 7.6), 7.36 (d, 1H, indole H7 , *J* = 8), ,6.92-6.82 (m, 3H, indole H2, H5, H6), 3.79 (s, 2H, C-CH2 -N), 3.20 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.68(t, 4H, piperazine H2, H6 , *J* = 4.8). Anal. Calc. for$C_{13}H_{17}N_3$: C, 77.35; H, 7.35; N, 14.42%, found:C, 78.16; H, 6.94; N, 14.25%, m/z:215.29

Ethyl 2-(3-piperazin-1-yl)methyl)-1H-indol-1-yl)acetate(4):

An equimolar mixture of 3-(piperzin-1-yl)methyl)-1H-indol(3) and chloro ethyl acetate were dissolved in dimethyl formamide solvent and to this reaction mixture anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature(35^{0}C) for 8 hours and the progress of the reaction was monitered by TLC using cyclohexane and ethylacetate solvent mixture (7:3) as eluent the reaction mixture was kept over night.After completion of the reaction the solvent was evaporated on rota-evaporater. The gummy solid was seperated and it was recrystalised from -2-propanol-petrolium ether(80^{0}c)solvent mixture.The crystaline solid was found to be -2-(3-formyl-1H-indol-1-yl)acetate. with a yield of 75% and mp 143-145^{0}C.The indole-3-carbaldehyde used in the present studies was purchased from aldrich company and was used without any forther purification. Yield 75%,m.p.:143-145^{0}C

Yield: 55%: mp 185.7 ^{0} C. IR (KBr) √ in cm−1 : 3150 (N-H), 3095-2782 (C-H). 1H-NMR (CDCl3): δ 7.60 (d, 1H, indole H4 , *J* = 7.6), 7.20 (d, 1H, indole H7 , *J* = 8), ,6.95-6.85 (m, 3H, indole H2, H5, H6), 3.85 (s, 2H, C-CH2 -N),

3.25 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.70(t, 4H, piperazine H2, H6 , *J* = 4.8), 1.29 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.13 (q, 2H, J=13.2Hz, CH_2 of ethyl group),. Anal. Calc. for $C_{17}H_{23}N_3O_2$: C, 78.32; H, 7.26; N, 14.42%, found:C, 78.18; H, 6.70; N, 14.15%, m/z:301.38

2-(3-((piperazin-1-yl)methyl)-1H-indol-1-yl)acetohydrazide(5):

A solution of 4 (0.01mol) and hydrazine hydrate (0.015) in ethanol (20ml) was refluxed for 5 hours.The reaction mixture was cooled and poured in to icecold water with stirring.The seperated solid was filtered, washed with water and recrystalised from ethanol.

Yield: 50%: mp 180.7 ^{0} C. IR (KBr) √ in cm^{-1} : 3160 (N-H), 3070-2780 (C-H). 1H-NMR (CDCl3): *δ*, 7.65 (d, 1H, indole H4 , *J* = 7.6), 7.35 (d, 1H, indole H7 , *J* = 8), ,6.80-6.85 (m, 3H, indole H2, H5, H6), 3.80 (s, 2H, C-CH2 -N), 3.25 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.70(t, 4H, piperazine H2, H6 , *J* = 4.8), ,4.28(s,2H,-NH_2),). 4.36 (s,2H N-CH_2-C =O), 4.98 (s,1 H,-N-NH), Anal. Calc. for $C_{15}H_{21}N_5O$: C, 78.32; H, 7.26; N, 14.42%, found:C, 78.18; H, 6.94; N, 14.25%, m/z:287.36

1-((phenyl (1,3,4-oxadiazol-2-yl)methyl)-3-(piperazine-1-yl)methyl)-1H-indole6(a):

A mixture of 2-(3-((piperazin-1-yl)methyl)-1H-indol-1-yl)acetohydrazide(5) (0.01 mol) and substituted corboxilic acid (0.01 mol) was heated at 100−120 oC in presence of excess polyphosphoric acid (PPA) for 4−5 h. After cooling, the mixture was poured into crushed ice, and neutralized with 5% aq.NaHCO3 solution. The precipitated solid was filtered and purified using column chromatography (petroleum ether:ethyl acetate, 9:1).

Yield: 60%: mp 190.7 ^{0} C. IR (KBr) √ in cm^{-1} : 3150 (N-H), 3050-2750 (C-H). 1H-NMR (CDCl3): *δ*, 7.65 (d, 1H, indole H4 , *J* = 7.6), 7.35 (d, 1H, indole H7 , *J* = 8), ,6.80-6.85 (m, 3H, indole H2, H5, H6), 7.35-7.45(m,5H,phenyl group),3.80 (s, 2H, C-CH2 -N), 3.25 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.70(t, 4H, piperazine H2, H6 , *J* = 4.8),, Anal. Calc. for $C_{22}H_{23}N_5O$: C, 78.32; H, 7.26; N, 14.42%, found:C, 78.18; H, 6.94; N, 14.25%, m/z:373.45

1-((tollyl (1,3,4-oxadiazol-2-yl)methyl))-3-(piperazine-1-yl)methyl)-1H-indole6(b):

Yield: 58%: mp 195.0 ^{0}C. IR (KBr) √ in cm^{-1} : 3100 (N-H), 3020-2720 (C-H). 1H-NMR (CDCl3): *δ*, 7.60 (d, 1H, indole H4 , *J* = 7.6), 7.30 (d, 1H, indole H7 , *J* = 8), 7.40-7.55(m,4H,phenyl group) ,6.60-6.65 (m, 3H, indole H2, H5, H6), 3.60 (s, 2H, C-CH2 -N), 3.75 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.50(t, 4H, piperazine H2, H6 , *J* = 4.8), 2.43(s,3H,-CH_3),2.40(s,3H,phenyl attached CH3 group) , Anal. Calc. for $C_{23}H_{25}N_5O$: C, 70.32; H, 7.15; N, 14.20%, found:C, 70.18; H, 6.94; N, 14.10%, m/z:387.48

1-((ethyl phenyl (1,3,4-oxadiazol-2-yl)methyl))-3-(piperazine-1-yl)methyl)-1H-indole6(c):

Yield: 52%: mp 192.0 ^{0} C. IR (KBr) √ in cm^{-1} : 3050 (N-H), 3010-2710 (C-H). 1H-NMR (CDCl3): *δ*, 7.25-7.65(m,4H,phenyl group) , 7.20 (d, 1H, indole H4 , *J* = 7.6), 7.10 (d, 1H, indole H7 , *J* = 8), ,6.20-6.35 (m, 3H, indole H2, H5, H6), 4.25(q,2H,of CH2,attached to phenyl gp),3.30 (s, 2H, C-CH2 -N), 3.15 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.40(t, 4H, piperazine H2, H6 , *J* = 4.8), 2.25(s,3H,-OCH_3),1.35(t,3H,CH3 of C_2H_5gp) , Anal. Calc. for $C_{24}H_{27}N_5O$: C, 65.32; H, 6.15; N, 12.20%, found:C, 65.18; H, 6.24; N, 12.10%. m/z:401.5

1-((chloro phenyl(1,3,4-oxadiazol-2-yl)methyl))-3-(piperazine-1-yl)methyl)-1H-indole6(d):

Yield: 53%: mp 160.0 ^{0} C. IR (KBr) √ in cm^{-1} : 3020 (N-H), 3090-2710 (C-H). 1H-NMR (CDCl3): *δ*, 7.10 (d, 1H, indole H4 , *J* = 7.6), 7.20 (d, 1H, indole H7 , *J* = 8), 7.15-7.40(m,4H,phenyl group),,6.20-6.15 (m, 3H, indole H2, H5, H6), 3.20(s, 2H, C-CH2 -N), 3.10 (t, 4H, piperazine H3, H5 , *J* = 4.8), 2.20(t, 4H, piperazine H2, H6 , *J* = 4.8),, Anal. Calc. for $C_{22}H_{22}ClN_5O$: C, 65.32; H, 6.15; N, 12.20%, found:C, 65.18; H, 6.24; N, 12.10%, m/z:407.9

1-((Bromo phenyl(1,3,4-oxadiazol-2-yl)methyl))-3-(piperazine-1-yl)methyl)-1H-indole6(e):

Yield: 51%: mp 165.0 ^{0} C. IR (KBr) √ in cm^{-1} : 3000 (N-H), 3010-2710 (C-H). 1H-NMR (CDCl3): δ, 7.15 (d, 1H, indole H4 , J = 7.6), 7.40 (d, 1H, indole H7 , J = 8), 7.05-7.25(m,4H,phenyl group), ,6.10-6.15 (m, 3H, indole H2, H5, H6), 3.10(s, 2H, C-CH2 -N), 3.15(t, 4H, piperazine H3, H5 , J = 4.8), 2.20(t, 4H, piperazine H2, H6 , J = 4.8),, Anal. Calc. for $C_{22}H_{22}BrN_5O$: C, 65.15; H, 6.15; N, 12.20%, found:C, 65.10; H, 6.04; N, 12.05%, m/z:453.35

1-((nitro phenyl(1,3,4-oxadiazol-2-yl)methyl))-3-(piperazine-1-yl)methyl)-1H-indole6(f):

Yield: 49%: mp 175.0 ^{0} C. IR (KBr) √ in cm^{-1} : 3020 (N-H), 3020-2750 (C-H). 1H-NMR (CDCl3): δ, 7.20 (d, 1H, indole H4 , J = 7.6), 7.00 (d, 1H, indole H7 , J = 8), 7.30-7.40(m,4H,phenyl group),,6.20-6.25 (m, 3H, indole H2, H5, H6), 3.15(s, 2H, C-CH2 -N), 3.20(t, 4H, piperazine H3, H5 , J = 4.8), 2.25(t, 4H, piperazine H2, H6 , J = 4.8),, Anal. Calc. for $C_{22}H_{22}N_6O3$,: C, 64.15; H, 4.15; N, 8.20%, found:C, 64.10; H, 4.04; N, 8.05%, m/z:418.5

Anti-Bacterial Activity:

The anti bacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcus aureus NCCS 2079 . The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of250 µglml and 500µglml using DMSO as a solvent the Cefaclor 10µglml disc was used as a standard .(Himedia,Laboratories Ltd, Mumbai).The test results presented in the table -1,suggest that 4b,4d,4e exhibit high activity against the tesed bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity:

The antifungal activities of synthesized compounds were studied by disc diffusion method against the organisms of Penicillium and Trichophton.

Compounds were treatd at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was Clotrimazole 50µglml against both organisms.The test results were presented in the table-2.

Table 1 Antibacterial activity by disc diffusion method of indolelinked 1,3,4oxadiazole. **4(a.f)**

Compound	Zone of inhibition (mm)			
	Staphylococcus aureus	**Bacillus cereus**	**Escherichia coli**	**Pseudomonas aeruginosa**
4a	16	18	13	12
4b	14	11	15	10
4c	13	12	10	09
4d	16	17	12	11
4e	18	16	15	17
4f	11	14	13	12
Cefaclor	19	22	19	20

.

Table 2 Antifungal activity by disc diffusion method for indole linked1,3,4oxadiazole 4(a-f)

Compound	Zone of inhibition (mm)	
	Asperigillus niger	Candida albicans
4a	14	16
4b	15	13
4c	17	15
4d	18	17
4e	23	21
4f	15	13
Clotrimazole	25-30	25-30

Conclusions

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The tetrazoles showed better antibacterial activity
3. 1,3,4 oxadiazole and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

Acknowledgement:

1. My sincere thanks to UGC authorities for providing financial assistance to continue research in better manner
2. I am very thankful to S.K. University authorities for providing such an environment for doing better research very much.
3. It's my pleasure to express my thanks to Department of Chemistry for giving an opportunity to do research.
4. I express my sincere thanks to my research Supervisor Prof P.Raveedra Reddy.
5. I express my sincere thanks to Prof LK Ravindranath, who is giving valuable guidance during my research.

References

[1] Brancale, A.; Silvestri, R. *Med. Res. Rev.* 2007, *27*, 209-238.
[2] Islam, M. N.; Iskander, M. N. *Mini Rev. Med. Chem.* 2004, *4*, 1077-1104.
[3] Bacher, G.; Beckers, T.; Emig, P.; Klenner, T.; Kutscher, B.; Nickel, B. *Pure Appl. Chem.* 2001, *73*, 1459-1464.
[4] Chang, J.; Hsieh, H.; Chang, C.; Hsu, K.; Chiang, Y.; Chen, C.; Kuo, C.; Liou, J. *J. Med. Chem.* 2006, *49*, 6656-6659.
[5] Liou, J.; Wu, Z.; Kuo, C.; Chang, C.; Lu, P.; Chen, C.; Hsieh, H.; Chang, J. *J. Med. Chem.* 2008, *51*, 4351-4355.
[6] Marchand, P.; Antoine, M.; Le Baut, G.; Czech, M.; Baasar, S.; Gunther, E. *Bioorg. Med. Chem.* 2009, *17*,6715-6727.
[7] Chen, J.; Lou, J.; Liu, T.; Wu, R.; Dong, X.; He, Q.; Yang, B.; Hu, Y. *Arch. Pharm. Chem. Life Sci.* 2009, *342*,165-172.
[8] Tung, Y.; Coumar, M. S.; Wu, Y.; Shio, H.; Chang J.; Liou, J.; Shukla, P.; Chang, C.; Chang, C.; Kuo, C.; Yeh,T.; Lin, C.; Wu, J.; Wu, S.; Liao, C.; Hsieh, H. *J. Med. Chem.* 2011, *54*, 3076-3080.
[9] Liou, J.; Chang, Y.; Kuo, F.; Chang, C.; Tseng, H.; Wang, C.; Yang, Y.; Chang, J.; Lee, S.; Hsieh, H. *J. Med. Chem.* 2004, *47*, 4247-4257.
[10] Kuo, C.; Hisieh, H.; Pan, W.; Chen, C.; Liou, J.; Lee, S.; Chang, Y.; Chen, L.; Chen, C.; Chang, J. *Cancer Res*.2004, *64*, 4621-4628.
[11] Liou, J. P.; Mahindroo, N.; Chang, C. W.; Guo, F. M.; Lee, S. W.; Tan, U. K.; Yeh, T. K.; Kuo, C. C.; Chang, Y. W.; Lu, P. H.; Tung, Y. S.; Tin, K. T.; Chang, J. Y. *ChemMedChem* 2006, *1*, 1106-1118.
[12] Andotra, C. S.; Manhas, B. S. Acta Cienc. Indica Chem.1992, 18, 99.
[13] Hutt, M. P.; Elstager, E. F.; Werbet, L. M. J. Heterocycl.Chem. 1970, 7, 511.

[14] Silvestrini, B.; Pagatti, C. Br. J. Pharmacol. 1961, 16, 209.
[15] Sharma, R. S.; Bahel, C. S. J. Indian Chem. Soc. 1982,59, 877.
[16] Omar, A.; Mohsen, M. E.; Aboul Wafa, O. M. J. Heterocycl.Chem. 1984, 21, 1415.
[17] Narayana, B.; Vijayaraj, K. K.; Ashalatha, B. V.; Kumari,N. S. Arch. Pharm. 2008, 338.
[18] Gaonkar, S. L.; Rai, K. M. Eur. J. Med. Chem. 2006, 41,841.
[19] Ali, M. A.; Yar, M. S. Bioorg. Med. Chem. Lett. 2007, 17,3314.
[20] Zarghi, A.; Tabatabai, S. A.; Faizi, M.; Ahadian, A.; Navabi,P.; Zanganeh, V.; Shafiee, A. Bioorg. Med.Chem. Lett.2005, 15, 1863.
[21] Bezerra, N. M. M.; De-Oliveira, S. P.; Srivastava, R. M.;Silva, D. Farmaco 2005, 60, 955.
[22] Zareef, M.; Iqbal, R.; De Dominguez, N. G.; Rodrigues,J.; Zaidi, J. H.; Arfan, M.; Supuran, C. T. J. Enzyme Inhib.Med. Chem. 2007, 22, 301.
[23] Ram, V. J.; Pandey, H. N. Eur. J. Med. Chem. 1990, 25,541.
[24] Shirote, P. J.; Bhatia, M. S. Arab. J. Chem. 2010, 145.
[25] Padmavathi, V.; Reddy, G. S.; Padmaja, A.; Kondaiah, P.;Shazia, A. Eur. J. Med. Chem. 2009, 44, 2106.
[26] Jayashankar, B.; Rai, K. M. L.; Baskaran, N.; Shazia, H.S. S. Eur. J. Med. Chem. 2009, 44, 3898.
[27] Shashikan, D.; Bhandari, V.; Bothara, K. G.; Raut, M. K.;Patil, A. A.; Sarkate, A. P.; Mokale, V. J. Bioorg. Med.Chem. Lett. 2008, 16, 1822.
[28] Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. Eur. J.Med. Chem. 1996, 31

Publication History
Received 24th July 2014
Revised 14th Aug 2014
Accepted 15th Sep 2014
Online 30th Sep 2014