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Research Article

SYNTHESIS AND CHARACTERIZATION OF NEW 7-HYDROXY-4-METHYL COUMARIN INCORPORATED FLAVANONE AND ISOXAZOLINE DERIVATIVES

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ABSTRACT

In the present study, new substituted isoxazolines (4a-c) have been synthesized *via* the simple and efficient reaction of flavanones (3a-c) with the hydroxyl amine hydrochloride in ethanol. The structures of the compounds were elucidated by elemental and spectral (IR, ^{1}HNMR, and MS) analysis. The reactions are easy to conduct, under mild conditions, and form coumarin substituted flavanones and isoxazolines in moderate to excellent yields.

Keywords: Flavanone, Isoxazoline, Coumarin, BVT.

1. INTRODUCTION

The coumarin skeleton is found in many natural products and is also used as a synthetic intermediate for the preparation of numerous heterocyclic compounds, possessing a wide spectrum of biological activities[1,2] such as antibacterial[3], antiviral, antitumor[4], anti-HIV and anti-inflammatory properties[5]. Particularly, isoxazoline is a five-membered heterocyclic which is a versatile lead compound for designing potent bioactive agents[6,7]. It is interesting to note from the chemical literature that isoxazoline derivatives showed various biological activities such as anti-microbial[8], anti-bacterial[9], anti-fungal[10], anti-stress[11], antinociceptive[12], anticonvulsant[13], analgesic[14], anti-influenza effects[15] and anti-inflammatory[16,17] activity. In addition, they showed a good potency in animal models of thrombosis[18] and played a crucial role in the theoretical development of heterocyclic chemistry.

Moreover, incorporation of fluorine can alter the course of the reaction as well as the biological activities. In addition, isoxazoline derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis[19–23].

In view of broad spectrum of biological applications of isoxazolines, this project was undertaken. Their high synthetic utility and pharmacological importance have prompted us to synthesize. Here in we report the synthesis of new isoxazolines.

2. EXPERIMENTAL

Melting points were determined on a Veego Melting Point apparatus Model no. VMP-DS with ± 0.5°C accuracy and are uncorrected. The ^{1}H NMR spectra were recorded on a BRUKER Spectrometer (400 MHz). Chemical shifts were reported in parts per million using TMS as an internal standard and were given in δ units. The solvent for NMR spectra was $CDCl_3$. Infrared spectra were taken on SHIMADZU-FTIR-8400 Spectrophotometer instrument in the frequency range of 4000-400 cm^{-1} by KBr powder method. The Mass spectra were recorded by MS-SHIMADZU-QP2010. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60F254 (Merk) plates using UV light (254 and 366 nm) for detection. Common reagent grade chemicals are either commercially available and were used without further purification.

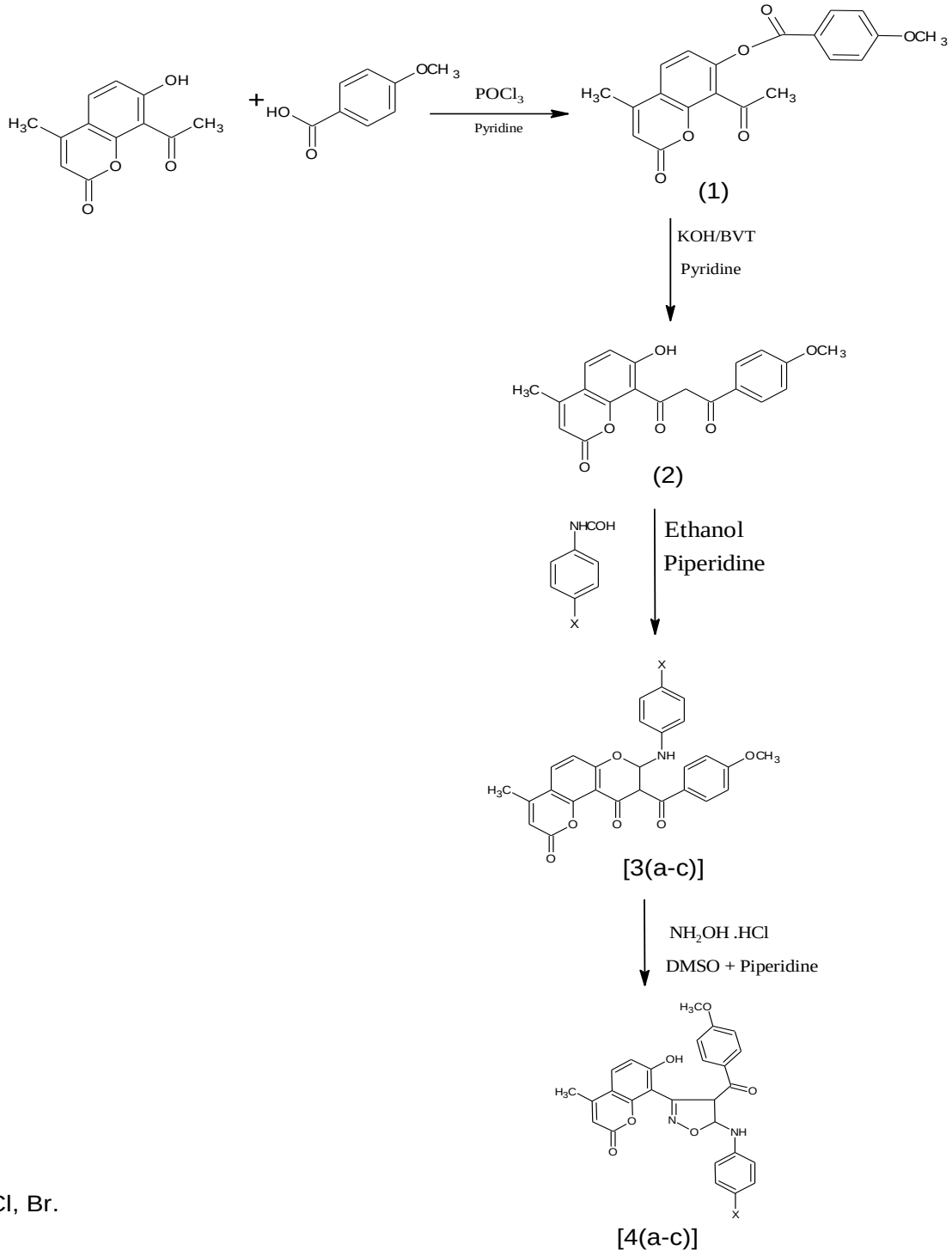
Synthesis of 8-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl 4-methoxybenzoate (1)

8-acetyl-7-hydroxy-4-methyl-2H-chromen-2-one (0.04mol) and 4-methoxy benzoic acid (0.05mol) were suspended in dry pyridine (30ml) and to this $POCl_3$ (3ml) was added drop wise with constant stirring and cooling. The reaction mixture was kept for overnight and

then worked up by dilution and acidification with ice cold HCl (50%) to neutralize pyridine. The solid product thus obtained was filtered washed with water followed by sodium carbonate (10%) washing and finally again with water. It was crystallized from ethanol-water mixture to obtain 8-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl 4-methoxybenzoate (1).

Pale yellow needles; yield- 66%; mp 150˚C; Elemental analysis calculated (%) for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.20; H, 4.52; IR spectrum (KBr), υ (cm^{-1}): 1490.34 (C=C str.), 1265.31 (C-O-C str. asym.), 1023.02 (C-O-C str. sym.), 1732.68 (ester C=O str.), 1645.28 (C=O str.). ^{1}HNMR spectrum (δ ppm): 2.42 (3H, d, CH_3); 2.48 (3H, s, CH_3); 3.90 (3H, s, OCH_3); 6.16-8.10 (Ar -CH).

REACTION SCHEME



X= F, Cl, Br.

Synthesis of 1-(2-hydroxy-3,5-dichlorophenyl)-3-(4'-methoxyphenyl)-1,3-propanedione (2)

This transformation called Base Catalyzed Baker-Venkatraman Transformation (BVT). 8-acetyl-4-methyl-2-oxo-2*H*-chromen-7-yl 4-methoxybenzoate (1) (0.05 mol) was dissolved in dry pyridine (40 ml). The solution was warmed at about 60˚C and pulverized KOH 15g was added slowly with constant stirring. The reaction mixture was heated at 125-130˚C in oil bath for 5-6 hours. After that the reaction mixture was acidified with ice cold dil. HCl (1:1). The solid product obtained was filtered washed with water followed by sodium carbonate (10%) washing and finally again with water. It was crystallized from ethanol-water mixture to get 1-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-3-(4-methoxyphenyl)propane-1,3-dione (2).

Brownish needles; yield- 63%; mp 180˚C; Elemental analysis calculated (%) for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.30; H, 4.42; IR spectrum (KBr), υ (cm^{-1}): 1498.15 (C=C str.), 1682.11 (C=O str.), 3155 (O=H str.). ^{1}HNMR spectrum (δ ppm): 2.3 (3H, d, CH_3); 3.77 (2H, s, CH_2); 3.78 (3H, s, OCH_3); 5.25 (1H, s, OH); 6.8-7.88 (Ar -CH).

Preparation of 8-((4-fluorophenyl) amino)-9-(4-methoxybenzoyl)-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (3a)

A mixture of 1-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl)-3-(4-methoxyphenyl) propane-1,3-dione (2) (0.01mol) and *N*-(4-fluorophenyl) formamide (0.012mol) was refluxed in ethanol(25ml) and piperidine (0.5 ml) at 70-80˚C in oil bath for 40-45 min. After cooling, the reaction mixture was acidified with dil HCl (1:1) and the product separated, was washed with water and crystallized from ethanol-water mixture to get the compound (3a).

Similarly the compound (3b) and (3c) synthesized by reacting *N*-(4-chlorophenyl) formamide and *N*-(4-bromophenyl) formamide respectively with compound (2).

8-((4-fluorophenyl) amino)-9-(4-methoxybenzoyl)-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (3a)

Off white needles; yield- 73%; mp 185˚C; Elemental analysis calculated (%) for $C_{27}H_{20}FNO_6$: C, 68.49; H, 4.26; N, 2.96. Found: C, 68.47; H, 4.33; N, 2.93; IR spectrum (KBr), υ (cm^{-1}): 1465.56 (C=C str.), 1259.54 (C-O-C str. asym.), 1024.68 (C-O-C str. sym.), 2984.16 (N-H str.), 1576.75 (N-H def.), 1676.35 (C=O str.), 1229.56 (C-F str.), 1324.50 (C-N str.). ^{1}HNMR spectrum (δ ppm): 2.4 (3H, d, CH_3); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 5.35 (1H, d, CH); 5.82 (1H, q, CH); 6.96-8.10 (Ar-CH).

8-((4-chlorophenyl)amino)-9-(4-methoxybenzoyl)-4-methyl-8,9-dihydropyrano [2,3-*f*]chromene-2,10-dione (3b)

Off white needles; yield- 67%; mp 190˚C; Elemental analysis calculated (%) for $C_{27}H_{20}ClNO_6$: C, 66.19; H, 4.11; N, 2.86. Found: C, 66.23; H, 4.15; N, 2.89; IR spectrum (KBr), υ (cm^{-1}): 1465.49 (C=C str.), 1259.16 (C-O-C str. asym.), 1024.39 (C-O-C str. sym.), 2939.06 (N-H str.), 1576.61 (N-H def.), 1675.36 (C=O str.), 771.41 (C-Cl str.), 1324.17 (C-N str.). ^{1}HNMR spectrum (δ ppm): 2.41 (3H, d, CH_3); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 5.37 (1H, d, CH); 5.82 (1H, q, CH); 6.96-8.10 (Ar-CH).

8-((4-bromophenyl)amino)-9-(4-methoxybenzoyl)-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (3c)

Off white needles; yield- 65%; mp 200˚C; Elemental analysis calculated (%) for $C_{27}H_{20}BrNO_6$: C, 60.69; H, 3.77; N, 2.62. Found: C, 60.63; H, 3.79; N, 2.65; IR spectrum (KBr), υ (cm^{-1}): 1465.78 (C=C str.), 1259.65 (C-O-C str. asym.), 1024.75 (C-O-C str. sym.), 2968.34 (N-H str.), 1576.41 (N-H def.), 1675.72 (C=O str.), 1324.68 (C-N str.). ^{1}HNMR spectrum (δ ppm): 2.4 (3H, d, CH_3); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 5.35 (1H, d, CH); 5.82 (1H, q, CH); 6.96-8.10 (Ar-CH).

Synthesis of 8-(5-((4- fluorophenyl) amino)-4-(4-methoxybenzoyl)-4,5-dihydro-isoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (4a)

A mixture of 8-((4-fluorophenyl) amino)-9-(4-methoxybenzoyl)-4-methyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (3a), (0.01 mol) and $NH_2OH.HCl$ (0.02 mol) was refluxed in DMSO (20ml) containing a few drops of piperidine (0.5 ml) at 195-200˚C in oil bath for about 1.5 hrs. After cooling, the reaction mixture was acidified with dil. HCl (1.1). The product separated was filtered, washed first with sodium bicarbonate solution (10%) and then with water. Finally it was crystallized from ethanol-water mixture to get the compound (4a).

Similarly (4b) and (4c) were synthesized by reaction of (3b) and (3c) with $NH_2OH.HCl$.

8-(5-((4-fluorophenyl)amino)-4-(4-methoxybenzoyl)-4,5-dihydroisoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (4a)

Off white needles; yield- 71%; mp 172˚C; Elemental analysis calculated (%) for $C_{27}H_{21}FN_2O_6$: C, 66.39; H, 4.33; N, 5.73. Found: C, 66.43; H, 4.37; N, 5.70.; IR spectrum (KBr), υ (cm^{-1}): 1465.49 (C=C str.), 842.97 (N-O str.), 1601.78 (C=N str.), 2920.50 (N-H str.), 1576.71 (N-H def.), 1676.71 (C=O str.), 1166.15 (C-F str.), 1297.81 (C-N str.), 3175.20 (O-H str.). ^{1}HNMR spectrum (δ ppm): 2.35 (3H, d, CH_3); 3.7 (1H, d, CH); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 4.7 (1H, q, CH); 5.4 (1H, s, OH); 6.96-8.10 (Ar-CH). Mass spectrum: 488.13 (M^+, 10%); 384.1066 (100%).

8-(5-((4-chlorophenyl) amino)-4-(4-methoxybenzoyl)-4,5-dihydroisoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (4b)

Off white needles; yield- 65%; mp 184˚C; Elemental analysis calculated (%) for $C_{27}H_{21}ClN_2O_6$: C, 64.23; H, 4.19; N, 5.55. Found: C, 64.20; H, 4.22; N, 5.58. IR spectrum (KBr), υ (cm^{-1}): 1465.70 (C=C str.), 843.25 (N-O str.), 1602.02 (C=N str.), 2981.01 (N-H str.), 1576.52 (N-H def.), 1676.02 (C=O str.), 771.31 (C-Cl str.), 1297.64 (C-N str.), 3112.20 (O-H str.). ^{1}HNMR spectrum (δ ppm): 2.41 (3H, d, CH_3); 3.72 (1H, d, CH); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 4.72 (1H, q, CH); 5.41 (1H, s, OH); 6.96-8.10 (Ar-CH). Mass spectrum: 504.57 (M^+, 15%); 384.1068 (100%).

8-(5-((4-bromophenyl) amino)-4-(4-methoxybenzoyl)-4,5-dihydroisoxazole-3-yl)-7-hydroxy-4-methyl-2H-chromen-2-one (4c)

Off white needles; yield- 68%; mp 174˚C; Elemental analysis calculated (%) for $C_{27}H_{21}BrN_2O_6$: C, 59.03; H, 3.85; N, 5.10. Found: C, 59.10; H, 3.91; N, 5.05; IR spectrum (KBr), υ (cm^{-1}): 1465.27 (C=C str.), 843.72 (N-O str.), 1601.93 (C=N str.), 2937.92 (N-H str.), 1576.87 (N-H def.), 1677.66 (C=O str.), 1297.35 (C-N str.), 3050.35 (O-H str.). ^{1}HNMR spectrum (δ ppm): 2.42 (3H, d, CH_3); 3.7 (1H, d, CH); 3.90 (3H, d, OCH_3); 4.1 (1H, d, NH); 4.71 (1H, q, CH); 5.45 (1H, s, OH); 6.96-8.10 (Ar-CH). Mass spectrum: 549.149 (M^+, 30%); 384.1065 (100%).

3. RESULTS AND DISCUSSION

The structures of compounds (3a-c) and (4a-c) were confirmed on the basis of spectral and elemental analysis. The IR spectrum of flavanones showed a band due to C-O-C asym. str. at (1259.16-1259.65 cm^{-1}), and C-O-C sym. str. (1024.39-1024.75 cm^{-1}), C=C str. (1665.49-1465.78 cm^{-1}), C=O str. (1675.36-1676.35 cm^{-1}), N-H str. (2939.06-2984.16 cm^{-1}), vibration band indicates formation of flavanone ring.

^{1}H-NMR ($CDCl_3$) spectrum of flavanone showed a signal at δ 5.35-5.37 (1H, d, C**H** flavanone ring) and δ 5.82 (1H, q, C**H** flavanone ring) confirms presence of flavanone ring. The IR spectrum of 4a-c exhibited a band due to OH str. (3050-3175 cm^{-1}), C=C str. (1465.27–1465.70 cm^{-1}), C=O str. (1676–1676.87 cm^{-1}), N–H str. (2920–2981 cm^{-1}), C–Cl str. (771.31 cm^{-1}), C–F str. (1166.15 cm^{-1}), C=N (ring) (1601–1602 cm^{-1}) and N-O (ring) (842-843.72 cm^{-1}) stretching vibration band which indicates the presence of the isoxazoline ring. Further, in their ^{1}H-NMR ($CDCl_3$) spectrum, the appearance of a signal at δ 3.7-3.72 (1H, d, C**H** isoxazoline) and δ 4.7-4.72 (1H, q, C**H**, isoxazoline) confirms the presence of isoxazoline ring.

4. CONCLUSION

The successful synthesis of flavanone and isoxazoline compounds follows a mild, efficient route with a good to moderate yield. In this research work we synthesized some isoxazolines by reacting flavanones with hydroxyl amine hydrochloride as the easily available substrates in DMSO and piperidine. Compounds with electron releasing groups such as methoxy group and having pharmacophores such as fluoro, chloro, bromo groups and both these groups are present in one moiety will show interesting biological activity, which we wish to manipulate further.

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REFERENCES

1. Paramjeet KM, Sharma D and Dubey A. Comparative Study of Microwave and Conventional Synthesis and Pharmacological activity of Coumarins : A Review. J Chem Pharm Res. 2012; 4(1):822-850
2. Mutalik V and Phaniband MA. Synthesis, characterization, fluorescent and antimicrobial properties of new Lanthanide(III) complexes derived from coumarin Schiff base. J Chem Pharm Res. 2011;3:313–330.
3. Olayinka OA and Obinna CN. Microwave-assisted synthesis and evaluation of antimicrobial activity of 3-{3-(s-aryl and s-heteroaromatic)acryloyl}-2H-chromen-

2-one derivatives. J Heterocycl Chem. 2010;47:179–187.
4. Hua Zuo, Geo Jose, Zhu-bo Li, Bu-Hyun Moon, Dong-Soo Shin and Manjunath Ghate. ARKIVOC. 2008;2:183–189.
5. More DH and Mahulikar PP. Microwave assisted one-pot synthesis of nitrogen and oxygen containing hetrocycles from acyl Meldrum's acid, Indian J Chem. 2011;50B:745–747.
6. Kaur H, Kumar S, Singh I and Kumar A. Inter J Pharm Sci Res. 2010;1:58–62.
7. Baseer MS, Shankaraiah GK, Omprakash SY and Bhaskar SD. A Facile Greener Assisted Protocol for the Synthesis of Some New 4-aryl-(5-chloro-3-Methyl-1-phenyl-1H-Pyrazol-4-yl)-4,5-dihydroisoxazol-3-yl) Derivatives and their in vitro Antimicrobial Activity. J Kor Chem Soc. 2012; 56:246–247.
8. Priya BS, Basappa and Rangappa KS. Δ2-isoxazoline derivatives as antimicrobials, Heterocycl. Commun. 2006;12:35.
9. Barbachyn MR, Cleek GJ, Dolak LA, Garmon SA, Morris J, Seest EP, Thomas RC, Toops DC, Watt W, Wishka DG, Ford CW, Zurenko GE, Hamel JC, Schaadt RD, Stapert D, Yagi BH, Adams WJ, Friis JM, Slatter JG, Sams JP, Oien NL, Zaya MJ, Wienkers LC and Wynalda MA. Identification of phenylisoxazolines as novel and viable antibacterial agents active against Gram-positive pathogens. J Med Chem. 2003;46:284-303.
10. Basappa, Sadashiva MP, Mantelingu K, Nanjunda Swamy S and Rangappa KS. Solution-phase synthesis of novel delta2-isoxazoline libraries via 1,3-dipolar cycloaddition and their antifungal properties. Bioorg Med Chem. 2003;11:4539-4544.
11. Rakesh M, Ausaf A, Prasoon G, Kailash C, Manmeet K, Jayendra R, Preeti R, Naila R and Gautam P. Synthesis of novel isoxazolines via 1,3-dipolar cycloaddition and evaluation of anti-stress activity. Med Chem Res. 2011;20:139–145
12. Karthikeyan K, Seelan VT, Lalitha KG and Perumal PT. Synthesis and antinociceptive activity of pyrazolyl isoxazolines and pyrazolyl isoxazoles. Bioorg Med Chem Lett. 2009;19:3370–3373.
13. Kaur H, Kumar S and Kumar A. Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/isoxazolinylindol-2-ones. Inter J Chem Tech Res. 2010;2:1010–1019.
14. Habeeb AG, Rao PNP and Knaus EE. Design and Synthesis of 4,5-Diphenyl-4-isoxazolines: Novel Inhibitors of Cyclooxygenase-2 with Analgesic and Antiinflammatory Activity. J Med Chem. 2001;44:2921–2927.
15. Kai H, Matsumoto H, Hattori N, Takase A, Fujiwara T and Sugimoto H. Anti-influenza virus activities of 2-alkoxyimino-n-(2-isoxazolin-3-ylmethyl)acetamides. Bioorg Med Chem Lett. 2001; 11:1997–2000.
16. Habeeb AG, Praveen Rao PN and Knaus EE. Design and synthesis of 4,5-diphenyl-4-isoxazolines: novel inhibitors of cyclooxygenase-2 with analgesic and antiinflammatory activity. J Med Chem. 2001;44:2921-2927.
17. Basappa, Satish Kumar M, Nanjunda Swamy S, Mahendra M, Shashidhara Prasad J, Viswanath BS and Rangappa KS. Novel delta2-isoxazolines as group II phospholipase A2 inhibitors. Bioorg Med Chem Lett. 2004;14:3679-3681.
18. Pinto JPD. J Med Chem. 2001;44:559–564.
19. Tomilovi YV, Okonnishnikova GP, Shulishov EV and Nefedov OM. Russ Chem Bull. 1995;44:2114.
20. Klimova EI, Marcos M, Klimova TB, Cecilio AT, Ruben AT and Lena RR. The structure of bicyclic ferrocenylmethylene substituted 2-pyrazolines and their reactions with azodicarboxylic acid N-phenylimide. J Organomet Chem. 1999;585:106-114.
21. Bhaskarreddy D, Padmaja A, Ramanareddy PV and Seenaiah B. Synthesis and reactivity of some new mono- and bis(2-pyrazolyl) sulfones, Sulfur Lett. 1993;16:227.
22. Padmavathi V, Sumathi RP, Chandrasekhar BN and Bhaskarreddy D. 1,3-Dipolar Cycloaddition of Dipolar Reagents to Bifunctional Olefins in the Presence of Chloramine-T (CAT). J Chem Res Synop. 1999;610-611.
23. Bhaskarreddy D, Chandrasekhar BN, Padmavathi V and Sumathi RP. Synthesis. 1998;491.