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Synthesis and Biological Evaluation of Furo[3,2-*c*]pyrazole-5-carbimidates

SRAVANTHI SILIVERI[1,2,*], HARINADHA BABU VAMARAJU[1] and SHIVARAJ[3]

[1]Department of Pharmaceutical Chemistry, G. Pulla Reddy College of Pharmacy, Mehidipatnam, Hyderabad-500028, India
[2]Department of Pharmacy, Osmania University College of Technology (OUCT), Osmania University, Hyderabad-500007, India
[3]Department of Chemistry, Osmania University, Hyderabad-500007, India

*Corresponding author: E-mail: sravanthisiliveri@gmail.com

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In the present work, novel pyrazole fused dihydrofurans synthesized *via* a chronological addition of *N*-chloro succinimide and base piperidine to pyrano[3,2-*c*]pyrazole carbonitrile derivatives in methanol medium. Oxidative difunctionalization was done with the reagent *N*-chloro succinimide by the addition of both chlorine and alkoxy groups crosswise the chromene double bond. The addition of base results in the construction of dihydrofuran derivatives by ring contraction. The structures of newly synthesized compounds were characterized on the basis of physical and spectral data. Synthesized compounds were evaluated for antibacterial and anti-inflammatory activities. All the compounds exhibited significant antibacterial activity against all the four strains of bacteria and their MICs ranged between 1.56 and 12.55 µg/mL. In anti-inflammatory screening, among all the tested compounds, compounds **7, 8, 9, 11, 12, 13, 14, 16, 17** and **18** exhibited significant protection against the edema formation at a concentration of 100 mg/kg.

Keywords: *N*-Chloro succinimide, Piperidine, Pyrano[3,2-*c*]pyrazole carbonitriles, Antibacterial activity, Anti-inflammatory activity.

INTRODUCTION

Pyrazoles have wide applications in the fields of agriculture as herbicides and insecticides as well as in pharmaceutical industry. Pyrazole derivatives have been reported to show a wide-ranging of biological activity together with antibacterial [1,2], antifungal [3], analgesic [4], anti-inflammatory, antidiabetic, neuroprotective, estrogen receptor binding, antineoplastic [5] activities. Due to their broad spectrum of biological activities, pyrazoles received a substantial interest in the area of drug discovery and therefore pyrazole ring constitutes an important synthetic target in pharmaceutical industry. On the other hand, furan, a five membered heterocycle containing oxygen as a hetero atom is a well known heterocyclic compound have an important attribute of a range of medicinal agents. The high therapeutic properties of the furan related drugs have encouraged the researchers to synthesize a large number of novel pharmacological agents which can act on various receptors in the body as MAO inhibitors [6], kappa opioid receptor agonist [7], sigma receptor agonist, γ-amino butyric acid receptor agonist, COX-2 inhibitor [8], β-blockers [9], muscarinic receptor agonist, α-adrenergic blockers, calcium channel blockers [10] *etc*. Furan drugs have broadened scope in remedying various dispositions in clinical medicines [11-15]. Apart from pyrazole and furan, annulated furo pyrazoles are important structural motifs in the domain of medicinal chemistry due to their myriad biological activities. Bi heterocyclic compounds in which pyrazole moiety is coupled with furan nucleus exhibit antimicrobial and anti-inflammatory activities. However there are no reports in literature concerning coupling of pyrazole ring with another biologically active furan nucleus either directly or through carbon bridge. In view of the above facts and in continuation of our research program [16] directed towards the development of a new, simple and less toxic biologically active molecules. The present work encompasses with dihydrofuro fused system of pyrazole ring to study the changes in biological activity. The current work presents, direct efficient and operationally convenient approach to the synthesis of some novel dihydrofuro fused pyrazole derivatives.

EXPERIMENTAL

All the chemicals used were of synthetic grade obtained from Sd fine, Spectrochem and Aldrich Chemicals. Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates. Visualization melting points were determined on ANALAB melting point apparatus and were uncorrected. All the ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solvents unless otherwise mentioned. Chemical shifts are reported on AVANCE 300 MHz and INNOVA 500 MHz spectrometers relative to TMS internal standard on the δ-scale. The IR spectra were recorded on Shimadzu FT-IR Spectrophotometer by using 1 % potassium bromide discs. The mass spectra were recorded on Quadruple mass spectrometry.

General procedures for the synthesis and spectral data of compounds (1-9): To a suspension of pyrano[3,2-*c*]pyrazole analogs (1 mmol) in 5 mL of methanol NCS (1.1 mmol) was added while stirring at room temperature open to air. The resulting clear is stirred at room temperature till the product precipitates out from it. The reaction mixture was filtered and washed with corresponding alcohol to separate the desired product. The structures of the products were assigned on the basis of the spectral data.

General procedures for the synthesis and spectral data of compounds (10-18): To a suspension of pyrano[3,2-*c*]pyrazole analogs (5 mmol) in alcohol (10 mL), *N*-chloro succinimide (5.5 mmol) was added at room temperature. After 3 h of stirring, piperidine (6 mmol) was added and stirred at same temperature for 5-6 h, till the product is completely precipitated out. The reaction mixture was filtered and washed with ethanol to separate the desired product (or) recrystallized from ethanol to afford the pure product.

5-Amino-6-chloro-5-methoxy-3-methyl-1,7-diphenyl-1,5,6,7-tetrahydropyrano[3,2-*c*]pyrazole-6-carbonitrile (1): Yellow solid; yield: 86 %; m.p.: 150-152 °C; IR (KBr, ν_{max}, cm^{-1}): 762, 1090, 3321.85 (N-H *str.*), 2195.70 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.78 (d, *J* = 7.74 Hz, 2H, Ar-H), 7.32 (t, 2H, Ar-H), 7.36-7.17 (m, 6H, Ar-H), 6.48 (brs, 2H, NH_2), 4.58 (s, 1H, 4-H), 3.50 (s, 3H, OCH_3), 1.83 (s, 3H, CH_3); Mass (ESI-MS): 395 $(M+H)^+$. Anal. calcd. for $C_{21}H_{19}N_4O_2Cl$ % calcd. (found): C, 63.88 (63.51); H, 4.85 (5.25); N, 14.19 (15.02); O, 8.10 (7.93); Cl, 8.98 (8.29).

5-Amino-6-chloro-5-methoxy-7-(4-methoxyphenyl)-3-methyl-1-phenyl-1,5,6,7-tetrahydro pyrano[3,2-*c*]pyrazole-6-carbonitrile (2): Yield: 90 %; m.p.: 163-165 °C; IR (KBr, ν_{max}, cm^{-1}): 772, 1090, 3390.63 (N-H *str.*) 2190.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.65 (brs, 2H, NH_2), 4.54 (s, 1H, 4-H), 4.01 (s, 3H, OCH_3), 3.41 (S, 3H, OCH_3) 1.82 (s, 3H, CH_3); Mass (ESI-MS): 426 $(M+2H)^+$. Anal. calcd. for $C_{21}H_{21}N_4O_3Cl$: C, 62.19 (62.32); H, 4.98 (4.55); N, 13.19 (12.98); O, 11.30 (12.13); Cl, 8.34 (8.02).

5-Amino-6-chloro-5-methoxy-7-(4-flourophenyl)-3-methyl-1-phenyl-1,5,6,7-tetrahydro pyrano[3,2-*c*]pyrazole-6-carbonitrile (3): Yield: 85 %; m.p.: 172-174 °C; IR (KBr, ν_{max}, cm^{-1}): 762, 1095, 3390.63 (N-H *str.*) 2180.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.65 (brs, 2H, NH_2), 4.54 (s, 1H, 4-H), 4.01 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 413 $(M+H)^+$. Anal. calcd. for $C_{21}H_{18}N_4O_2ClF$ % calcd. (found): C, 61.09 (60.85); H, 4.39 (4.50); N, 13.57 (13.27); O, 7.75 (8.18); F, 4.60 (4.81); Cl, 8.59 (8.39).

5-Amino-6-chloro-5-methoxy-7-(4-bromophenyl)-3-methyl-1-phenyl-1,5,6,7-tetrahydro pyrano[3,2-*c*]pyrazole-6-carbonitrile (4): Yield: 85 %; m.p.: 183-185 °C; IR (KBr, ν_{max}, cm^{-1}): 762, 1095, 3370.63 (N-H *str.*) 2200.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.42 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.18-6.7 (m, 5H, Ar-H) 6.50 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.30 (brs, 2H, NH_2), 4.58 (s, 1H, 4-H), 3.42 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 474 $(M+H)^+$. Anal. calcd. for $C_{21}H_{18}N_4O_2BrCl$ % calcd. (found): C, 53.24 (53.46); H, 3.83 (4.02); N, 11.83 (12.39); O, 6.75 (6.85); Br, 16.87 (16.30); Cl, 7.48 (6.98).

5-Amino-6-chloro-5-methoxy-7-(4-nitrophenyl)-3-methyl-1-phenyl-1,5,6,7-tetrahydropyrano[3,2-*c*]pyrazole-6-carbonitrile (5): Yield: 80 %; m.p.: 165-167 °C; IR (KBr, ν_{max}, cm^{-1}): 762, 1095, 3391.43 (N-H *str.*) 2202.39 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.20 (d, *J* = 8.30 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.12 Hz, 2H, Ar-H), 7.55-7.38 (m, 4H, Ar-H), 7.25 (t, 1H, Ar-H), 6.97 (s, 2H, NH_2), 4.78 (s, 1H, 4H), 3.6 (s, 3H, OCH_3) 1.84 (s, 3H, CH_3); Mass (ESI-MS): 440 $(M+H)^+$. Anal. calcd. for $C_{21}H_{18}N_5O_4Cl$ % calcd. (found): C, 57.34 (56.98); H, 4.12 (4.32); N, 15.92 (15.50); O, 14.55 (15.03); Cl, 8.06 (8.17).

5-Amino-6-chloro-5-methoxy-7-(4-methylphenyl)-3-methyl-1-phenyl-1,5,6,7-tetrahydropyrano[3,2-*c*]pyrazole-6-carbonitrile (6): Yield: 86 %; m.p.: 152-154 °C; IR (KBr, ν_{max}, cm^{-1}): 772, 1090, 3390.63 (N-H *str.*) 2190.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.65 (brs, 2H, NH_2), 4.54 (s, 1H, 4-H), 3.41 (S, 3H, OCH_3), 2.03 (s, 3H, CH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 409 $(M+H)^+$. Anal. calcd. for $C_{22}H_{21}N_4O_2Cl$ % calcd. (found): C, 64.62 (64.73); H, 5.18 (5.30); N, 13.70 (13.01); O, 7.83 (8.02); Cl, 8.67 (8.94).

5-Amino-6-chloro-5-methoxy-3-methyl-7-(3-phenoxyphenyl)-1-phenyl-1,5,6,7-tetrahydropyrano[3,2-*c*]pyrazole-6-carbonitrile (7): Yield: 75 %; m.p.: 182-184 ºC; IR (KBr, ν_{max}, cm^{-1}): 762, 1095, 3288.19 (N-H *str.*) 2193.58 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.77 (d, *J* = 8.30 Hz, 2H, Ar-H), 7.41 (t, 2H, Ar-H), 7.35-7.19 (m, 4H, Ar-H), 7.11-6.81 (m, 6H, Ar-H), 6.46 (brs, 2H, NH_2), 4.58 (s, 1H, 4-H), 3.61 (s, 3H, OCH_3) 1.90 (s, 3H, CH_3); Mass (ESI-MS): 487 $(M+H)^+$. Anal. calcd. for $C_{27}H_{23}N_4O_3Cl$ % calcd. (found): C, 66.60 (66.26); H, 4.76 (5.22); N, 11.51 (12.17); O, 9.86 (9.23); Cl, 7.28 (7.012).

5-Amino-6-chloro-5-methoxy-3-methyl-1-phenyl-7-(thiophen-2-yl)-1,5,6,7-tetrahydro pyrano[3,2-*c*]pyrazole-6-carbonitrile (8): Yield: 82 %; m.p.: 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 762, 1085, 3356.87 (N-H *str.*) 2189.52 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 7.42 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.18-6.7 (m, 4H, Ar-H) 6.50 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.30 (brs, 2H, NH_2), 4.58 (s, 1H, 4-H), 3.42 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 401 $(M+H)^+$. Anal. calcd. for $C_{19}H_{17}N_4O_2SCl$ % calcd. (found): C, 56.93 (56.64); H, 4.27

(4.35); Cl, 8.84 (8.75); N, 13.98 (13.70), O, 7.98 (8.35), S, 8.00 (8.21).

5-Amino-6-chloro-5-methoxy-3-methyl-1-phenyl-7-(pyridin-3-yl)-1,5,6,7-tetrahydropyrano[3,2-*c*]pyrazole-6-carbonitrile (9): Yield: 75 %; m.p.: 195-197 °C; IR (KBr, ν_{max}, cm^{-1}): 782, 1085, 3364.66 (N-H *str.*), 2190.81 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.50 (d, *J* = 4.34 Hz, 2H, Ar-H), 7.79 (d, *J* = 7.74 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.74 Hz, 1H, Ar-H) 7.51 (t, 2H, Ar-H), 7.44-7.23 (m, 4H, 2H-NH_2, 2H-Ar-H), 4.79 (s, 1H, 4-H), 3.5 (s, 3H, OCH_3), 1.79 (s, 3H, CH_3); Mass (ESI-MS): 396 $(M+H)^+$. Anal. calcd. for $C_{20}H_{18}N_5O_2Cl$ % calcd. (found): C, 60.68 (60.34); H, 4.58 (4.84); N, 17.69 (18.02); O, 8.08 (8.15); Cl, 8.96 (8.65).

Methyl-5-cyano-3-methyl-1,6-diphenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (10): Yield: 80 %; m.p.: 170-172 °C; IR (KBr, ν_{max}, cm^{-1}): 1090, 1672, 3321.85 (N-H *str.*), 2195.70 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.41 (s, 1H, NH), 7.78 (d, *J* = 7.74 Hz, 2H, Ar-H), 7.32 (t, 2H, Ar-H), 7.36-7.17 (m, 6H, Ar-H), 4.58 (s, 1H, 4-H), 3.50 (s, 3H, OCH_3), 1.83 (s, 3H, CH_3); Mass (ESI-MS): 359 $(M+H)^+$; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO), δ ppm: 174.1, 155.1, 150.0, 140.0, 135.1, 127.5, 128.1, 125.1, 124.3, 120.2, 119.4, 115.2, 112.2, 76.2, 58.2, 48.8, 8.1; Anal. calcd. for $C_{21}H_{18}N_4O_2$ % calcd. (found): C, 70.38 (70.36); H, 5.06 (5.08); N, 15.63 (15.61); O, 8.93 (8.95).

Methyl-5-cyano-6-(4-methoxyphenyl)-3-methyl-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (11): Yield: 80 %; m.p.: 185-187 °C; IR (KBr, ν_{max}, cm^{-1}): 1090, 1670, 3390.63 (N-H *str.*) 2190.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.5 (s, 1H, NH), 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 4.54 (s, 1H, 4-H), 4.01 (s, 3H, OCH_3), 3.60 (S, 3H, OCH_3) 1.82 (s, 3H, CH_3); Mass (ESI-MS): 389 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 174.5, 156.1, 153.0, 147.5, 140.0, 141.2, 131.1, 126.1, 125.3, 118.2, 117.5, 110.2, 108.2, 76.2, 58.2, 53.1, 48.5, 9.2; Anal. calcd. for $C_{22}H_{20}N_4O_3$ % calcd. (found): C, 68.03 (68.05); H, 5.19 (5.17); N, 14.42 (14.44); O, 12.36 (12.34).

Methyl-5-cyano-6-(4-flourophenyl)-3-methyl-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (12): Yield: 85 %; m.p.: 192-194 °C; IR (KBr, ν_{max}, cm^{-1}): 1095, 1684, 3390.63 (N-H *str.*) 2180.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.6 (s, 1H, NH), 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 4.54 (s, 1H, 4-H), 4.01 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 377 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) ppm: 175.0, 160.1, 151.2, 145.2, 140.2, 141.3, 128.2, 123.2, 122.3, 117.6, 116.0, 115.1, 112.5, 75.1, 58.2, 48.2, 9.1; Anal. calcd. for $C_{21}H_{17}N_4O_2F$ % calcd. (found): C, 67.01 (67.03); H, 4.55 (4.53); N, 14.89 (14.90); O, 8.50 (8.50); F, 5.05 (5.04).

Methyl-5-cyano-6-(4-bromophenyl)-3-methyl-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (13): Yield: 82 %; m.p.: 202-204 °C; IR (KBr, ν_{max}, cm^{-1}): 1670, 1095, 3370.63 (N-H *str.*) 2200.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.4 (s, 1H, NH), 7.42 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.18-6.7 (m, 5H, Ar-H) 6.50 (d, *J* = 8.89 Hz, 2H, Ar-H), 4.58 (s, 1H, 4-H), 3.42 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 438 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 175.0, 151.2, 145.2, 140.2, 141.3, 128.2, 123.2, 122.3, 120.3, 117.6, 116.0, 115.1, 112.5, 75.1, 58.2, 48.2, 9.1; Anal. calcd. for $C_{21}H_{17}N_4O_2Br$ % calcd. (found): C, 57.68 (57.66); H, 3.92 (3.94); Br, 18.27 (18.25); N, 12.81 (12.82); O, 7.32 (7.33).

Methyl-5-cyano-6-(4-nitrophenyl)-3-methyl-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (14): Yield: 81 %; m.p.: 188-190 °C; IR (KBr, ν_{max}, cm^{-1}): 1683, 1095, 3391.43 (N-H *str.*) 2202.39 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.51 (s, 1H, NH), 8.20 (d, *J* = 8.30 Hz, 2H, Ar-H), 7.80 (d, *J* = 8.12 Hz, 2H, Ar-H), 7.55-7.38 (m, 4H, Ar-H), 7.25 (t, 1H, Ar-H), 4.78 (s, 1H, 4-H), 3.6 (s, 3H, OCH_3) 1.84 (s, 3H, CH_3); Mass (ESI-MS): 404 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 175.0, 156.1, 151.2, 145.2, 140.2, 141.3, 128.2, 123.2, 122.3, 117.6, 116.0, 115.1, 112.5, 75.1, 58.2, 48.2, 9.1; Anal. calcd. for $C_{21}H_{17}N_5O_4$ % calcd. (found): C, 62.53 (62.55); H, 4.25 (4.23); N, 17.36 (17.38); O, 15.86 (15.84).

Methyl-5-cyano-6-(4-methylphenyl)-3-methyl-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (15): Yield: 80 %; m.p.: 182-184 °C; IR (KBr, ν_{max}, cm^{-1}): 1680, 1090, 3390.63 (N-H *str.*) 2190.98 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.4 (s, 1H, NH), 7.79 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.42 (t, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.14 (d, *J* = 8.89 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.89 Hz, 2H, Ar-H), 4.54 (s, 1H, 4-H), 3.41 (S, 3H, OCH_3), 2.03 (s, 3H, CH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 409 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 174.5, 156.1, 153.0, 147.5, 140.0, 135.8, 131.1, 126.1, 125.3, 118.2, 117.5, 110.2, 108.2, 76.2, 58.2, 48.5, 25.2, 9.2; Anal. calcd. for $C_{22}H_{20}N_4O_2$ % calcd. (found): C, 70.95 (70.93); H, 5.41 (5.43); N, 15.04 (15.06); O, 8.59 (8.57).

Methyl-5-cyano-3-methyl-6-(3-phenoxyphenyl)-1-phenyl-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (16): Yield: 75 %; m.p.: 210-212 °C; IR (KBr, ν_{max}, cm^{-1}): 1682, 1095, 3288.19 (N-H *str.*) 2193.58 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.41 (s, 1H, NH), 7.77 (d, *J* = 8.30 Hz, 2H, Ar-H), 7.41 (t, 2H, Ar-H), 7.35-7.19 (m, 4H, Ar-H), 7.11-6.81 (m, 6H, Ar-H), 4.58 (s, 1H, 4-H), 3.61 (s, 3H, OCH_3), 1.90 (s, 3H, CH_3); Mass (ESI-MS): 451 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 175.4, 159.1, 158.5, 155.3, 144.2, 143.3, 144.1, 129.1, 128.3, 127.5, 124.3, 121.2, 120.2, 119.4, 118.5, 117.2, 115.5, 112.2, 110.1, 73.2, 52.3, 37.5, 12.1; Anal. calcd. for $C_{27}H_{22}N_4O_3$ % calcd. (found): C, 71.99 (71.97); H, 4.92 (4.94); N, 12.44 (12.45); O, 10.65 (10.64).

Methyl-5-cyano-3-methyl-1-phenyl-6-(thiophen-2-yl)-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (17): Yield: 78 %; m.p.: 230-232 °C; IR (KBr, ν_{max}, cm^{-1}): 1685, 1085, 3356.87 (N-H *str.*) 2189.52 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.2 (s, 1H, NH), 7.42 (d, *J* = 7.90 Hz, 2H, Ar-H), 7.18-6.7 (m, 4H, Ar-H) 6.50 (d, *J* = 8.89 Hz, 2H, Ar-H), 4.58 (s, 1H, 4-H), 3.42 (s, 3H, OCH_3), 1.82 (s, 3H, CH_3); Mass (ESI-MS): 365 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 174.5, 153.0, 147.5, 140.0, 141.2, 131.1, 126.1, 125.3, 118.2, 117.5, 110.2, 108.2, 76.2, 58.2, 53.1, 48.5, 9.2; Anal. calcd. for $C_{19}H_{16}N_4O_2S$ % calcd. (found): C, 62.62 (62.60); H, 4.43 (4.44); N, 15.37 (15.38); O, 8.78 (8.79); S, 8.80 (8.79).

Methyl-5-cyano-3-methyl-1-phenyl-6-(pyridin-3-yl)-5,6-dihydro-1*H*-furo[3,2-*c*]pyrazole-5-carbimidate (18):

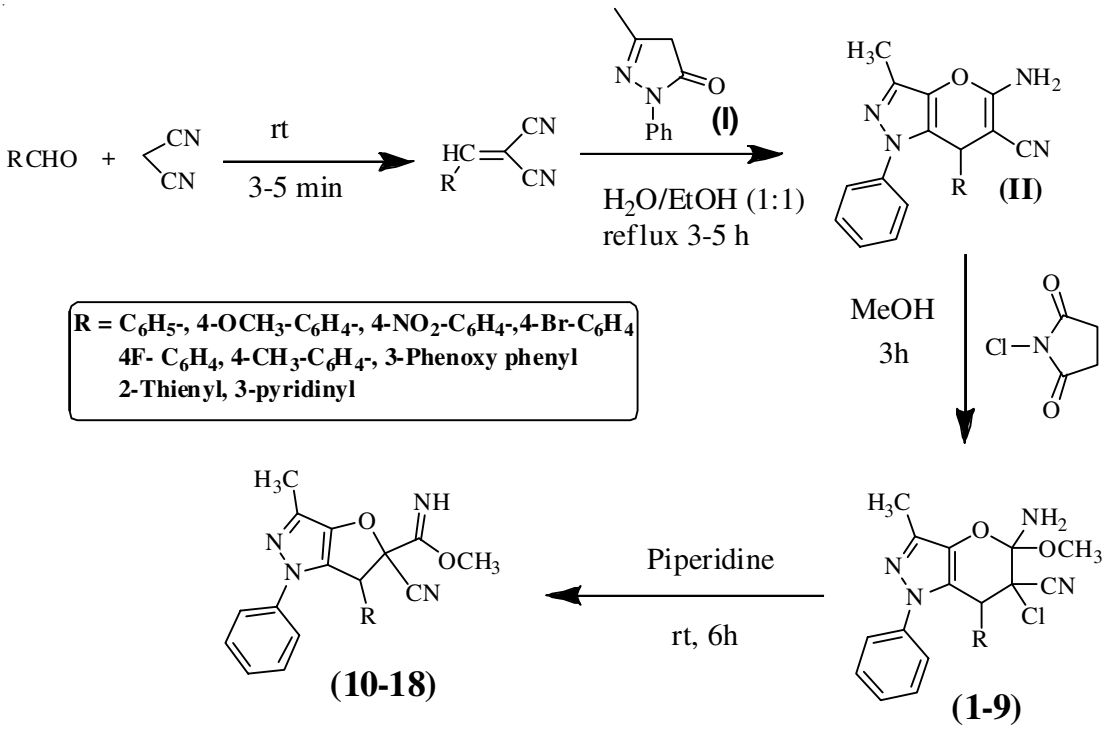
Yield: 75 %; m.p.: 195-197 °C; IR (KBr, ν_{max}, cm^{-1}): 1680, 1085, 3364.66 (N-H *str.*), 2190.81 (C≡N *str.*); ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.55 (s, 1H, NH), 7.79 (d, *J* = 7.74 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.74 Hz, 1H, Ar-H) 7.51 (t, 2H, Ar-H), 7.44-7.23 (m, 4H, Ar-H), 4.79 (s, 1H, 4-H), 3.42 (s, 3H, OCH_3), 1.79 (s, 3H, CH_3); Mass (ESI-MS): 360 $(M+H)^+$, ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ ppm: 175.0, 156.1, 149.4, 146.9, 142.7, 140.7, 138.5, 133.5, 133.0, 130.0, 127.2, 125.9, 124.3, 120.0, 76.3, 55.7, 40.2, 9.5; Anal. calcd. for $C_{20}H_{17}N_5O_2$ % calcd. (found): C, 66.84 (66.86); H, 4.77 (4.75); N, 19.49 (19.48); O, 8.90 (8.91).

RESULTS AND DISCUSSION

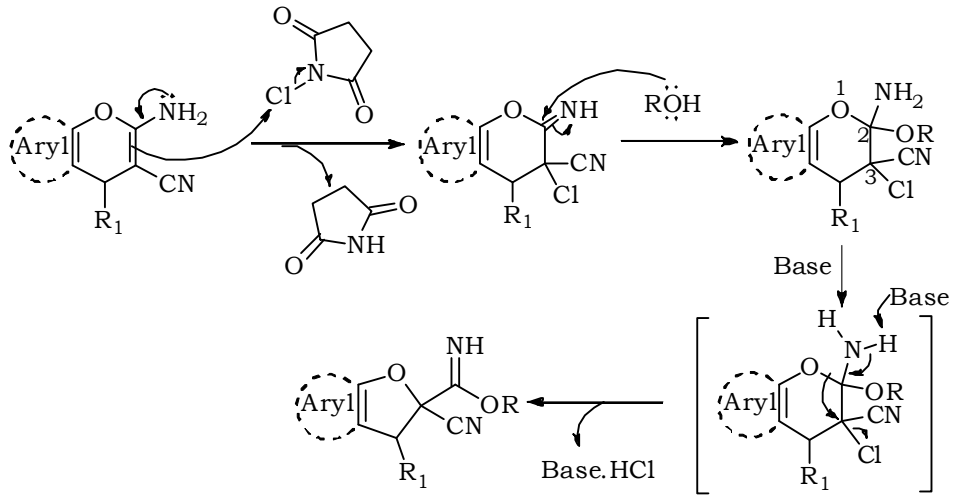
The synthetic route of title compounds [(**1-9**) and (**10-18**)] is shown in **Scheme-I**. Oxidative difunctionalization of pyrano[3,2-*c*]pyrazole carbonitriles was done with NCS reagent in methanol medium. In this reaction with NCS addition of both chlorine and alkoxy groups takes place crosswise the chromene double bond and resulted the products (**1-9**). Annexes to this, compounds (**10-18**) were synthesized *via* dehydrohalogenation on compounds (**1-9**) with piperidine as a base in solvent methanol at room temperature. The reaction mixture turned to a clear brown coloured solution, followed by the precipitation of product after 6 h. The structures of newly synthesized compounds were characterized on the basis of physical and spectral data. The possible mechanism for the synthesis of compounds (**10-18**) is shown in **Scheme-II**.

Biological evaluation

Antibacterial activity: All the synthesized compounds were screened for antibacterial activity against four strains of bacteria, *Bacillus subtilis* and *Staphylococcus aureus* (Gram-



Scheme-I: Synthetic route for the compounds (**1-18**)



Scheme-II: Mechanism for the synthesis of compounds (**10-18**)

TABLE-1
ANTIBACTERIAL ACTIVITY OF DIFFERENT COMPOUNDS BY BROTH MICRO DILUTION MIC METHOD

µg/mL	Antibacterial activity against standard strains–compounds																											
	Compound **7**				Compound **8**				Compound **9**				Compound **11**				Compound **12**				Compound **17**				Compound **18**			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
0.3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1.5	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	–	–	+	+	+	+	+	+
3.1	–	–	–	–	+	+	+	+	–	–	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
6.2	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
12.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
25	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
50	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
100	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

1 = *Bacillus subtilis*; 2 = *Staphylococcus aureus*; 3 = *Escherichia coli*; 4 = *Pseudomonas aeruginosa*; + Resistant; – Susceptible.
Ciprofloxacin is taken as a standard drug and its MIC is 1.56 µg/mL against all the four strain.

positive), *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative) using ciprofloxacin as a standard drug as per the reported methods [17-19] and MICs were determined at different concentrations 0.39, 0.78, 1.56, 3.125, 6.25, 12.5, 25, 50, 100 µg/mL by using Broth Micro dilution MIC method [20]. Among all, compounds **7, 8, 9, 11, 12, 17** and **18** showed antibacterial activity against all the four strains of bacteria and their MICs ranged between 1.56 and 12.55 µg/mL. The results are tabulated in Table-1.

Anti-inflammatory activity: Ten compounds were tested for anti-inflammatory activity by Plethysmography. From the data obtained, the mean paw edema volume and percentage reduction in edema was calculated. All the compounds were found to possess good anti-inflammatory activity and represented in Table-2.

TABLE-2
PERCENTAGE PROTECTION AGAINST EDEMA FORMATION

Treatment	Dose (mg/kg)	Protection against edema formation (%)				
		0.5 h	1 h	2 h	3 h	4 h
Standard (Ibuprofen)	100	37	42.6	51.7	71.3	63.4
7	100	22.4	39.8	51.8	65.5	50.6
8	100	30.4	50.5	66.1	72.0	53.9
9	100	16.6	34.3	46.9	67.6	62.5
11	100	24.0	44.2	63.3	71.9	54.8
12	100	22.5	35.1	55.7	68.8	51.6
13	100	12.7	27.7	43.4	52.7	48.3
14	100	11.7	30.5	43.8	56.9	50.5

Conclusion

The present work intended at synthesizing the structurally different dihydrofuran derivatives *via* an one pot reaction of pyrano[2,3-*c*]pyrazole carbonitriles with *N*-chloro succinimide and base piperidine. The purity and structures of the synthesized compounds were confirmed by physical and spectral data (IR, NMR and Mass). All the compounds were tested for antibacterial and anti-inflammatory activities. Among all the tested compounds, **7, 8, 9, 11, 12, 17** and **18** showed anti bacterial activity against both Gram-positive and Gram-negative standard strains and their MICs ranged between 1.56 and 12.55 µg/mL. In anti-inflammatory studies all the compounds exhibited good percentage protection against edema formation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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