Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(24): 1-11
(http://www.derpharmachemica.com/archive.html)

A Facile Synthesis and Pharmacological Evolution of Pyranopyrazole-Naphthoquinone Hybrids as Antimicrobial and Anticancer Agents

Venkata Swamy Tangeti[1,2*], Boyi Harika Reddy[1], Palla Sombabu[3]

[1]Raghu Engineering College, Visakhapatnam, Andhra Pradesh-531162, India
[2]Vector Control Research Centre (Indian Council of Medical Research), Puducherry-605006, India
[3]Avanthi Institute of Engineering and Tecnology, Vishakapatnam, India.

ABSTRACT

A series of antibacterial active pyranopyrazole-napthaquinone hybrids are synthesized from one pot condensation of sulphonated β-keto ester, simple β-keto ester, aromatic aldehyde, hydrazine in presence of piperidine catalyst under ethanol solvent conditions and subsequent replacement of SO_2Ph group with 2-hydroxy naphthoquinone. We have conducted Structure Activity Relationship (SAR) studies based on initial antimicrobial screening of a set of twenty three conjugates against four bacterial strains (Bacillus subtilis, Escherichia coli, Staphylococcus epidermidis and Proteus vulgaris) and five antifungal stains (Aspergillus flavus, Monascus purpureus, Aspergillus niger, Penicillium citrinum and Candida albicans). SAR studies revealed that compounds 11d, 11e, 11r, 11s, 11t, 11u, 11v were found to be more active in antimicrobial screening. Anti-proliferative properties were evaluated against Du145, A549, FaDu human cancer cell lines. Among the derivatives MeO and CF_3 substituted hybrid molecules 11r, 11s, 11t, 11u, 11v showed most potent cytotoxic activity against all four cancer cell lines.

Keywords: Pyranopyrazole-napthaquinone, Sulphonated β-Keto ester, Blaise reaction, Triflouro, Trimethoxy, 2-Hydroxy napthaquinone

INTRODUCTION

Both pyranopyrazoles and napthaquinones are widely distributed heterocyclic natural products with varied biological activities. Pyranopyrazoles exhibit analgesic, anti-inflammatory activity and act as vasodilators as well as hypotensive and hypoglycemic agents [1,2]. Plants containing napthaquinones have been employed in folk medicine for the treatment of many diseases, especially among Indian population [3]. Napthaquinone derivatives are acts as antiplasmodial, trypanocidal, antimalarial agents [4,5]. At the border between bio-inspired design and rational design, one can imagine preparation of hybrid molecules with a dual mode of action to create efficient new drugs. In this Account, hybrid molecules are defined as chemical entities with two or more structural units having different biological functions and dual activity, indicating that a hybrid molecule acts as two distinct pharmacophores. Several hybrid molecules show multiple activities (Figure 1A) [6-9].

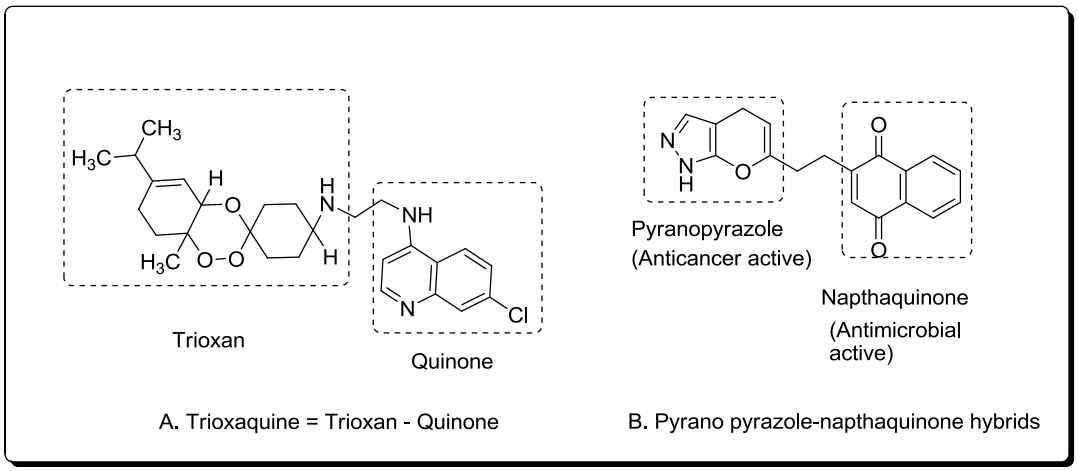


Figure 1: (A) Commercially available hybrid molecule trioxane, (B) Structure of pyranopyrazole-napthaquinone hybrids

In medicinal field pyranopyrazoles and napthaquinones, independently, find extensive use. Moreover, pyranopyrazole-napthaquinone hybrids, target molecules of present study are not known. Synthesis of such heterocyclic entities holds promise for integrating medicinal and fluorescent properties. In the continuous efforts towards the synthesis of different biologically active heterocyclic molecules [10-17] recently our group has developed novel methodologies for synthesis of C3-substituted dihydrofuran coumarin, dihydrofuron pyrazoles under microwave-irradiation. Similarly we have developed coumarin flavone hybrids as anticancer agents by the synergic property of both the entities. Now we are contemplated to synthesize pyranopyrazole-napthaquinone derivatives to explore their integrated antimicrobial activity Figure 1A and 1B.

EXPERIMENTAL SECTION

General

The progression of all the reactions was monitored by TLC using a solution of hexanes (60-80°C boiling mixture) and ethyl acetate as eluent. ^{1}H-NMR spectra (400 MHz) and ^{13}C-NMR (100 MHz) and DEPT-135 spectra were recorded for (DMSO-D_6 and DMSO-d_6 + CCl_4; 1:1) solutions on a Bruker-400 spectrometer with Tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Number of hydrogen's attached to each carbon was determined from DEPT spectra and are given next to the corresponding ^{13}C-NMR spectral data. IR spectra were recorded as KBr pellets on a Nicolet-6700 spectrometer. Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. High resolution mass spectra were recorded on a Waters Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use.

General procedure for synthesis of ethyl 3-methyl-4-phenyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8a

To a stirred aqueous mixture of hydrazine hydrate 96% 7 (34 mg, 0.692 mmol) and ethyl acetoacetate 5 (100 mg, 0.692 mmol), benzaldehyde 6 (73 mg, 0.692 mmol), ethyl 3-oxo-5-(phenylthio)-pentanoate 5 (0.132 g, 2 mmol) and piperidine (6 mg, 0.069 mmol) were added successively at room temperature under an open atmosphere with vigorous stirring for 5-10 min. The precipitated solid was filtered, washed with water and then with a mixture of ethyl acetate/ hexane (30:70). Products were further purified by recrystallization from cold ethanol solution. Yellow Colour, Yield 85%, Mp 123.4°C, IR (KBr)υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.51 (br s, 1H), 7.41-7.20 (m, 10H), 4.51 (s, 1H), 4.20 (q, *J*=7.8 Hz, H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.5, 142.5, 138.9, 136.7, 129.4, 129.0, 128.9, 128.5, 125. 7, 125.3, 113.4, 101.8, 62.4, 36.4, 33.2, 27.6, 14.4, 13.2 ppm; HRMS (ESI, m/z): 443.1405 calcd for $C_{24}H_{24}N_2O_3S$ (M+Na) found: 443.1403. Analysis calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66; S, 7.63; Found C, 68.53; H, 5.72; N, 6.68; S, 7.61.

Ethyl 4-(4-chlorophenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8b: Yellow Colour, Yield 83%, M.p. 125.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), 12.59 (br s, 1H), 7.39 (d, *J*=7.8 Hz, H), 7.39 (d, *J*=8.2 Hz, H), 7.37 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.22-7.17 (m, 3H), 4.20 (q, *J*=7.8 Hz, H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 140.4, 137.3, 136.7, 131.2, 130.4, 129.3, 128.9, 125.8, 125.1, 113.4, 101.4, 61.7, 37.5, 33.0, 27.7, 14.3, 13.4 ppm; HRMS (ESI, m/z): 477.1016 calcd for $C_{24}H_{23}ClN_2O_3S$ (M+Na) found: 477.1015. Analysis calcd for $C_{24}H_{23}ClN_2O_3S$, C, 63.36; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05. Found C, 63.36; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05.

Ethyl 4-(2-chlorophenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8c: Yellow Colour, Yield 89%, M.p. 125.2°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), 12.59 (br s, 1H), 7.65 (t, *J*=7.2 Hz, H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (d, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.4, 163.7, 162.6, 144.6, 139.1, 136.4, 131.8, 129.3, 128.9, 128.7, 127.1, 126.7, 125.1, 113.4, 61.4, 61.7, 33.1, 32.4, 27.7, 14.2, 13.1 ppm; HRMS (ESI, m/z): 477.1016 calcd for $C_{24}H_{23}ClN_2O_3S$ (M+Na) found: 477.1014. Analysis calcd for $C_{24}H_{23}ClN_2O_3S$: C, 63.36; H, 5.10; Cl, 7.79; N, 6.16; S, 7.05; Found C, 63.34; H, 5.08; N, 6.17; S, 7.02.

Ethyl 4-(2,6-dichlorophenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8d: Yellow Colour, Yield 82%, M.p. 134.2°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.59 (br s, 1H), 7.45 (t, *J*=8.4 Hz, 1H), 7.39 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.21 (t, *J*=7.8 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 1H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ=167.2, 163.7, 162.8, 139.1, 138.5, 136.4, 135.7, 129.3, 128.9, 127.5, 126.8, 125.1, 113.4, 101.4, 61.7, 33.1, 27.7, 27.3 14.2, 13.1 ppm; HRMS (ESI, m/z): 511.0626 calcd for $C_{24}H_{22}Cl_2N_2O_3S$ (M+Na) found: 511.0624. Analysis calcd for $C_{24}H_{22}Cl_2N_2O_3S$: C, 58.90; H, 4.53; N, 5.72; S, 6.55; Found C, 58.90; H, 4.53; N, 5.72; S, 6.55.

Ethyl-3-methyl-6-(2-(phenylthio)ethyl)-4-(2,4,6-trichlorophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8e: Yellow Colour, Yield 78% (551 mg), M.p. 139.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.57 (br s, 1H), 7.58 (s, 2H),7.35-7.31 (m, 4H), 7.24 (m, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.96 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 139.2, 137.3, 136.2, 134.1, 129.3, 128.4, 128.1, 125.0, 113.8, 101.3, 62.3, 33.5, 27.6, 27.2, 14.2, 13.2 ppm; HRMS (ESI, m/z): 545.0236 calcd for $C_{24}H_{21}Cl_3N_2O_3S$ (M+Na) found: 545.0231. Analysis calcd for $C_{24}H_{21}Cl_3N_2O_3S$: C, 72.35; H, 4.55; N, 7.03; Found C, 55.03; H, 4.04; N, 5.35; S, 6.12. $C_{24}H_{21}Cl_3N_2O_3S$, C, 55.03; H, 4.04; N, 5.35; S, 6.12.

Ethyl 4-(4-bromophenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8f: Yellow Colour, Yield 88%, M.p. 138.7°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.56 (br s, 1H), 7.85 (d, *J*=8.2 Hz, H), 7.39 (d, *J*=8.0 Hz, 2H), 7.35 (m, 2H), 7.21 (m, 1H), 7.12 (d, *J*=8.0 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ=167.2, 163.7, 162.8, 141.3, 139.1, 136.7, 131.5, 131.2, 129.3, 128.9, 125.1, 120.1, 113.4, 101.4, 61.7, 37.5, 33.1, 27.7, 14.3, 13.6 ppm; HRMS (ESI, m/z): 521.0510 calcd for $C_{24}H_{23}BrN_2O_3S$ (M+Na) found: 521.0507. Analysis calcd for $C_{24}H_{23}BrN_2O_3S$: C, C, 57.72; H, 4.64; N, 5.61; S, 6.42; Found C, 57.70; H, 4.63; N, 5.59; S, 6.40.

Ethyl 3-methyl-6-(2-(phenylthio)ethyl)-4-p-tolyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8g: Yellow Colour, Yield 88%, M.p. 145.2°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.54 (br s, 1H), 7.39 (d, *J*=7.8 Hz, 2H), 7.35 (m, 2H), 7.21 (m, 1H), 7.11-7.9 (m, 4H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 2.34 (s, 3H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=168.0, 163.4, 162.7, 139.3, 139.1, 136.4, 135.1, 129.1, 128.7, 125.5, 125.1, 113.4, 101.4, 61.7, 37.5, 33.4, 27.1, 21.2, 14.3, 13.0 ppm; HRMS (ESI, m/z): 457.1556 calcd for

$C_{25}H_{26}N_2O_3S$ (M+Na) found: 457.1552. Analysis calcd for $C_{25}H_{26}N_2O_3S$: C, 69.10; H, 6.03; N, 6.45; S, 7.38; Found C, 69.08; H, 6.01; N, 6.40; S, 7.35.

Ethyl 4-(2,4-dimethylphenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8h: Yellow Colour, Yield 85%, M.p. 147.8°C, IR (KBr), υ_{max}=3116, 3005, 2983, 1791, 1648, 1465, 1381, 1212, 1094, 815, 786, 727cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.58 (br s, 1H), 7.39 (d, *J*=6.8 Hz, 2H), 7.35 (t, *J*=6.8 Hz, 2H), 7.21 (m, 1H), 6.98 (d, *J*=7.2 Hz, 1H), 6.96 (s, 1H), 6.92 (d, *J*=7.2 Hz, 1H), 4.94 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.34 (t, *J*=7.6 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 139.1, 136.7, 136.4, 135.9, 135.3, 130.8, 129.3, 128.9, 128.7, 125.8, 125.2, 113.4, 101.4, 61.7, 35.0, 33.1, 27.8, 21.6, 19.8, 14.2, 13.2 ppm; HRMS (ESI, m/z): 471.1718 calcd for $C_{26}H_{28}N_2O_3S$ (M+Na) found: 471.1715. Analysis calcd for $C_{26}H_{28}N_2O_3S$: C, 69.62; H, 6.29; N, 6.24; S, 7.15; Found C, 69.60; H, 6.25; N, 6.22; S, 7.11.

Ethyl 4-(4-(dimethylamino)phenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8i: Yellow Colour, Yield 79%, M.p. 152°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.48 (br s, 1H), 7.39 (t, *J*=8.4 Hz, 2H), 7.35 (t, *J*=8.0 Hz, 2H), 7.20 (m, 2H), 7.05 (d, *J*=8.0 Hz, 2H), 6.67 (d, *J*=7.8 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.06 (s, 6H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 163.5, 147.9, 139.2, 136.4, 131.8, 129.8, 129.3, 128.9, 125.1, 113.4, 112.8, 101.4, 61.4, 41.5, 37.5 ppm; HRMS (ESI, m/z): 486.1822 calcd for $C_{26}H_{29}N_3O_3S$ (M+Na) found: 486.1821 Analysis calcd for $C_{26}H_{29}N_3O_3S$: C, 67.36; H, 6.31; N, 9.06; Found C, 67.34; H, 6.30; N, 9.03.

Ethyl 4-(4-hydroxyphenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8j: Yellow Colour, Yield 91%, M.p. 152.6°C, IR (KBr). υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ=12.64 (br s, 1H), 10.23 (br s, 1H), 7.39 (t, *J*=8.2 Hz, 2H), 7.35 (t, *J*=8.2 Hz, 2H), 7.21 (m, 1H), 7.06 (d, *J*=7.8 Hz, 2H), 6.63 (d, *J*=7.8 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.4, 163.5, 162.8, 155.4, 139.3, 136.7, 134.9, 130.4, 129.3, 128.5, 125.1, 115.8, 113.4, 101.4, 61.7, 37.5, 33.1, 27.7, 14.4, 13.2 ppm; HRMS (ESI, m/z): 459.1349 calcd for $C_{24}H_{24}N_2O_4S$ (M+Na) found: 459.1346. Analysis calcd for $C_{24}H_{24}N_2O_4S$: C, 66.03; H, 5.54; N, 6.42; S, 7.35; Found C, 66.01; H, 5.52; N, 6.41; S, 7.33.

Ethyl 4-(4-methoxyphenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8k: Yellow Colour, Yield 90%, M.p. 130.1°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ=12.64 (br s, 1H), 7.39 (t, *J*=7.6 Hz, 2H), 7.35 (t, *J*=7.6 Hz, 2H), 7.21 (m, 1H), 7.12 (d, *J*=6.8 Hz, 2H), 6.87 (d, *J*=6.8 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.83 (s, 3H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.0, 163.7, 162.8, 155.6, 139.0, 136.7, 134.7, 130.2, 129.3, 128.9, 125.1, 115.8, 113.4, 101.4, 61.6, 37.4, 33.0, 27.7, 14.4, 13.2 ppm;; HRMS (ESI, m/z): 450.1613 calcd for $C_{25}H_{26}N_2O_4S$ (M+Na) found: 450.1611. Analysis calcd for $C_{25}H_{26}N_2O_4S$: C, 66.64; H, 5.82; N, 6.22; S, 7.12; Found C, 66.62; H, 5.80; N, 6.21; S, 7.11.

Ethyl 4-(3,4-dimethoxyphenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8l: Yellow Colour, Yield 88%, M.p. 138.4°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.62 (br s, 1H), 7.37 (t, *J*=7.8 Hz, 2H), 7.34 (t, *J*=7.8 Hz, 2H), 7.20 (m, 1H), 6.76 (d, *J*=6.8 Hz, 1H), 6.69 (s, 1H), 6.68 (d, *J*=6.8 Hz, 1H) 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.4, 162.9, 162.5, 149.7, 146.8, 139.1, 136.4, 130.9, 129.3, 128.6, 125.1, 122.3, 113.4, 112.6, 112.0, 101.4, 61.6, 56.2, 56.1, 37.8, 33.1, 27.7, 14.6, 13.0 ppm; HRMS (ESI, m/z): 480.1719 calcd for $C_{26}H_{28}N_2O_5S$ (M+Na) found: 480.1717. Analysis calcd for $C_{26}H_{28}N_2O_5S$: C, 64.98; H, 5.87; N, 5.83; S, 6.67; Found C, 64.97; H, 5.85; N, 5.81; S, 6.64.

Ethyl 3-methyl-4-(4-nitrophenyl)-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8m: Yellow Colour, Yield 81%, Mp 147.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.60 (br s, 1H), 8.14 (d, *J*=8.0 Hz, 2H), 7.49 (d, *J*=7.8 Hz, 2H), 7.39 (d, *J*=7.8 Hz, 2H), 7.35 (d, *J*=7.2 Hz, 2H), 7.21 (t, *J*=7.2 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 1H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (d, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ=167.2, 163.4, 162.8, 148.2, 144.9, 139.1, 136.4, 129.9, 129.3, 128.6, 125.1, 123.8, 113.4, 101.4, 61.4, 37.6, 33.1 ppm; HRMS (ESI, m/z): 488.1251 calcd for $C_{24}H_{23}N_3O_5S$ (M+Na) found: 488.1249. Analysis calcd for $C_{24}H_{23}N_3O_5S$: C, 61.92; H, 4.98; N, 9.03; S, 6.89; Found C, 61.91; H, 4.96; N, 9.01; S, 6.87.

Ethyl 3-methyl-4-(3-nitrophenyl)-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8n: Yellow Colour, Yield 88%, M.p. 146.7°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.47 (br s, 1H), 8.12 (s, 1H), 8.08 (d, *J*=8.4 Hz, 1H), 7.68 (d, *J*=7.8 Hz, 1H), 7.59 (m, 1H), 7.39-7.35 (m, 5H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 147.8, 147.6, 139.1, 136.4, 133.3, 129.3, 128.9, 125.1, 121.8, 120.9, 120.7, 113.4, 101.4, 61.7, 36.5, 33.1, 27.7, 14.2, 13.3 ppm; HRMS (ESI, m/z): 488.1251 calcd for $C_{24}H_{23}N_3O_5S$ (M+Na) found: 488.1249. Analysis calcd for $C_{24}H_{23}N_3O_5S$: C, 61.92; H, 4.98; N, 9.03; S, 6.89; Found C, 61.90; H, 4.96; N, 9.01; S, 6.88.

Ethyl 4-(furan-2-yl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8o: Yellow Colour, Yield 83%, M.p. 157.2°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.58 (br s, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.39 (d, *J*=8.0 Hz, H), 7.35 (t, *J*=8.4 Hz, 2H), 7.21 (m, 1H), 6.40 (t, *J*=6.8 Hz, 1H), 6.08 (d, *J*=6.8 Hz, 1H), 4.97 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.3, 163.7, 162.8, 152.5, 142.1, 139.1, 136.4, 129.3, 128.9, 125.1, 113.4, 110.6, 106.7, 101.4, 61.7, 32.5, 29.5, 27.7, 14.2, 12.5 ppm; HRMS (ESI, m/z): 433.1192 calcd for $C_{22}H_{22}N_2O_4S$ (M+Na) found: 433.1190. Analysis calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82; S, 7.81; Found C, 64.35; H, 5.39; N, 6.80; S, 7.80.

Ethyl 3-methyl-6-(2-(phenylthio)ethyl)-4-(thiophen-2-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8p: Yellow Colour, Yield 84%, M.p. 146.6°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 12.68 (br s, 1H), 7.40 (d, *J*=8.4 Hz, 1H), 7.39 (d, *J*=8.4 Hz, 2H), 7.35 (t, *J*=7.8 Hz, 2H), 7.21 (m, 2H), 6.93 (t, *J*=7.0 Hz, 1H), 6.83 (d, *J*=7.0 Hz, 1H), 4.65 (s, 1H), 4.18 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ=167.2, 163.8, 162.6, 139.4, 139.1, 136.4, 129.3, 128.9, 127.0, 126.7, 125.5, 125.1, 113.0, 101.4, 61.6, 33.1, 29.2, 27.5, 14.2, 13.0 ppm; HRMS (ESI, m/z): 426.1072 calcd for $C_{22}H_{22}N_2O_3S_2$ (M+Na) found: 426.1070. Analysis calcd for $C_{22}H_{22}N_2O_3S_2$: C, 61.95; H, 5.20; N, 6.57; S, 15.03; Found C, 61.93; H, 5.18; N, 6.55; S, 15.01.

Ethyl 3-methyl-6-(2-(phenylthio)ethyl)-4-(pyridin-2-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8q: Yellow Colour, Yield 91%,

M.p. 145.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 12.62 (br s, 1H), 8.49 (d, *J*=8.0 Hz, 1H), 7.65 (t, *J*=7.8 Hz, 1H), 7.39 (d, *J*=7.8 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 7.24 (t, *J*=6.8 Hz, 1H), 7.21 (m, 1H), 7.18 (d, *J*=6.8 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 158.6, 148.6, 139.1, 136.4, 136.2, 129.3, 128.6, 125.1, 124.1, 120.9, 113.4, 101.4, 61.7, 33.1, 28.3, 27.7, 14.2, 13.0 ppm; HRMS (ESI, m/z): 444.1358 calcd for $C_{23}H_{23}N_3O_3S$ (M+Na) found: 444.1357. Analysis calcd for $C_{23}H_{23}N_3O_3S$: C, 72.35; H, 4.55; N, 7.03; Found C, 72.33; H, 4.54; N, 7.01.

Ethyl 3-methyl-6-(2-(phenylthio)ethyl)-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8r: Yellow Colour, Yield 78%, M.p. 138.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.62 (br s, 1H), 7.50 (d, *J*=8.0 Hz, 2H), 7.39 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=8.0 Hz, H), 7.21 (m, 1H), 7.16 (d, *J*=6.8 Hz, 2H), 7.16 (d, *J*=6.8 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.5, 145.5, 138.9, 136.4, 129.4, 129.3, 128.0, 125.1, 125.0, 124.1, 113.4, 101.2, 61.7, 37.5, 33.1, 27.7, 14.2, 13.1 ppm; HRMS (ESI, m/z): 511.1274 calcd for $C_{25}H_{23}F_3N_2O_3S$ (M+Na) found: 511.1272. Analysis calcd for $C_{25}H_{23}F_3N_2O_3S$: C, 61.46; H, 4.75; F, 11.67; N, 5.73; S, 6.56; Found, C, 61.46; H, 4.75; F, 11.67; N, 5.73; S, 6.56.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-3-methyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 8s: Yellow Colour, Yield 88%, M.p. 141.5°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=12.59 (br s, 1H), 7.43 – 7.40 (m, 2H), 7.39-7.35 (m, 4H), 7.21 (m, 1H), 7.16 (d, *J*=7.8 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.2, 163.7, 162.8, 139.1, 138.6, 136.2, 132.6, 129.3, 128.6, 127.1, 125.0, 124.9, 123.8, 123.4, 123.3, 120.9, 113.4, 101.4, 61.7, 37.5, 33.2, 27.6, 14.2, 13.0 ppm; HRMS (ESI, m/z): 579.1148 calcd for $C_{26}H_{22}F_6N_2O_3S$ (M+Na) found: 579.1145. Analysis calcd for $C_{26}H_{22}F_6N_2O_3S$: C, 56.11; H, 3.98; N, 5.03; S, 5.76; Found C, 56.10; H, 3.96; N, 5.02; S, 5.74.

Ethyl 3-methyl-6-(2-(phenylthio)ethyl)-4-(2,4,5-tris(trifluoromethyl)phenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 8t: Yellow Colour, Yield 78%, Mp 156.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 12.62 (br s, 1H), 7.69 (s, 1H), 7.39 (d, *J*=7.8 Hz, 2H), 7.35 -7.32 (m, 3H), 7.21 (m, 1H), 4.72 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.95 (t, *J*=7.2 Hz, 2H), 2.30 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=167.1, 163.5, 162.4, 139.1, 138.3, 136.1, 134.2, 129.2, 128.7, 127.6, 127.1, 125.0, 124.3, 123.7, 123.6, 123.2, 121.0, 113.2, 101.2, 61.2, 35.2, 33.0, 27.7, 14.3, 13.1 ppm; HRMS (ESI, m/z): 647.1021 calcd for $C_{27}H_{21}F_9N_2O_3S$ (M+Na) found: 647.1019. Analysis calcd for $C_{27}H_{21}F_9N_2O_3S$: C, 51.93; H, 3.39; N, 4.49; S, 5.13; Found C, 51.91; H, 3.38; N, 4.47; S, 5.11.

General procedure for synthesis of ethyl 3-methyl-4-phenyl-6-(2-(phenylsulfonyl) ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 9a

To a stirred solution of ethyl 3-methyl-4-phenyl-6-(2-(phenylthio)ethyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 8a (290 mg, 0.692 mmol) in $CHCl_3$ (10 ml) at –40°C was added 50-60% m-CPBA (0.61 g, 1.8 mmol) in $CHCl_3$ (10 ml) dropwise via addition funnel. This solution was stirred at –40 °C for 12 h and then was allowed to warm to 0°C in the refrigerator overnight. Then, the solution was cooled to –40°C for 1 h and was filtered to remove any excess m-CPBA. The filtrate was washed with 2 M NaOH (3 × 25 ml), brine (25 ml), and was dried with Na_2SO_4. Organic layer was concentrated by rotaevoparation. Pure yellow colour crystalline solid was obtained by recrystallization from EtOH. Yield (295 mg) 95%, MP.157.4°C.

General procedure for synthesis of pyranopyrazole-napthaquinone hybrids (11a-x)

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 11a: A mixture of ethyl 3-methyl-4-phenyl-6-(2-(phenylsulfonyl) ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 9a (312 mg, 0.692 mmol), 2-Hydroxy Naphthoquinone **10a** (120 mg, 0.69 mmol) in EtOH (5 ml), was stirred at room temperature for 5 mins. Piperidine (6 mg, 0.069 mmol) were added sequentially to the mixture and it was refluxed at 80°C for 20 min till the completion of the reaction (monitored by TLC). After completion of reaction ethanol was distilled out and in the product crushed ice (25 g) was added. To this 0.5 M HCl (1 ml) was added and the resulting aqueous with suspended solids was extracted with dichloromethane (2 × 10 ml) and concentrated. Crude product was purified through column chromatography (TLC, 30% EtOAc in hexanes; Rf=0.23). After recrystallization from EtOH, product obtained as yellow color crystalline solid. Yield 92%, Mp 161.1°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.65 (br s, 1H), 12.60 (br s, 1H), 8.04 (d, *J*=7.8 Hz, 2H),7.82 (d, *J*=8.0 Hz, 2H),7.33 (m, 2H), 7.26 (m, 1H), 7.23 (d, *J*=8.0 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.00 (t, *J*=7.2 Hz, 2H), 1.98 (t, *J*=7.2 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.2, 163.7, 162.8, 154.2, 142.3, 139.1, 135.0, 131.8, 130.8, 129.1, 128.6, 126.8, 125.7, 121.9, 113.2, 101.4, 61.5, 37.2, 29.8, 15.0, 14.2 ppm; HRMS (ESI, m/z): 507.1527 calcd for $C_{28}H_{24}N_2O_6$ (M+Na) found: 507.1526. Analysis calcd for $C_{28}H_{24}N_2O_6$: C, 69.41; H, 4.99; N, 5.78; Found C, 69.40; H, 4.96; N, 5.75.

Ethyl 4-(4-chlorophenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11b: Light yellow colour solid, Yield 93%, M.p. 169.1°C, IR (KBr). υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.45 (br s, 1H), 12.56 (br s, 1H), 7.92- 7.90 (m, 2H), 7.60-7.58 (m, 2H), 7.37 (d, *J*=7.6 Hz, 2H), 7.17 (d, *J*=7.8 Hz, 2H),4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7.2 Hz, H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.8, 167.2, 163.7, 162.8, 154.0, 140.4, 139.1, 135.0, 134.9, 131.8, 131.3, 130.8, 130.4, 126.8, 126.7, 125.8, 121.9, 113.4, 101.4, 61.5, 37.4, 29.9, 15.0, 14.2, 13.1 ppm; HRMS (ESI, m/z): 541.1137 calcd for $C_{28}H_{23}ClN_2O_6$ (M+Na) found: 541.1134. Analysis calcd for $C_{28}H_{23}ClN_2O_6$: C, 64.80; H, 4.47; N, 5.40; Found C, 64.78; H, 4.44; N, 5.39.

Ethyl 4-(2-chlorophenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11c: Light yellow colour solid, Yield 80%, M.p. 174.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.51 (br s, 1H), 7.92-7.90 (m, 2H), 7.59-7.57 (m, 2H), 7.55 (d, *J*=8.0 Hz, 2H), 7.21-7.17 (m, 3H), 4.74 (s, 3H), 4.20 (q, *J*=7.8 Hz, 2H), 2.01 (t, *J*=7.2 Hz, 2H), 1.98 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.31 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184., 181.5, 167.2, 163.7, 162.8, 154.2, 144.5, 139.3, 135.1, 135.0, 131.8, 131.7, 130.5, 128.3, 127.7, 127.2, 126.8, 126.7, 121.9, 113.5, 101.5, 61.5, 32.1, 29.8, 15.3, 14.5, 13.2 ppm; HRMS (ESI, m/z): 541.1137 calcd for $C_{28}H_{23}ClN_2O_6$ (M+Na) found: 541.1134. Analysis calcd for $C_{28}H_{23}ClN_2O_6$: C, 64.80; H, 4.47; N, 5.40; Found C, 64.78; H, 4.44; N, 5.39.

Ethyl 4-(2,6-dichlorophenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11d: Light yellow colour solid, Yield 89%, M.p. 174.2°C, IR (KBr) υ_{max} 3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.58 (br s, 1H), 12.57 (br s, 1H), 7.92-7.90 (m, 2H), 7.60 (m, 2H), 7.53 (m, 2H), 7.45

(m, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7.2 Hz, 2H), 1.95 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.3, 163.5, 162.6, 154.0, 139.1, 135.7, 135.5, 135.0, 134.9, 131.8, 130.7, 126.7, 126.4, 121.9, 113.4, 101.4, 61.7, 29.9, 27.1, 15.0, 14.1, 12.9 ppm; HRMS (ESI, m/z): 575.0747 calcd for $C_{28}H_{22}Cl_2N_2O_6$ (M+Na) found: 575.0745. Analysis calcd for $C_{28}H_{22}Cl_2N_2O_6$: C, 60.77; H, 4.01; N, 5.06; Found C, 60.75; H, 4.00; N, 5.03.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-ethyl)-3-methyl-4-(2,4,6-trichlorophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11e: Light yellow colour solid, Yield 86%, M.p. 177.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.61 (br s, 1H), 12.58 (br s, 1H), 7.92 (m, 2H), 7.60 -5.57 (m, 2H), 7.56 (d, *J*=8.2 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.03 (t, *J*=7.2 Hz, 2H), 2.01 (t, *J*=7.2 Hz, 2H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.2, 163.7, 162.8, 154.1, 139.1, 137.1, 136.6, 135.0, 134.9, 134.0, 131.8, 130.5, 128.3, 126.5, 121.9, 113.5, 101.3, 61.7, 29.9, 27.3, 15.1, 14.2, 13.0 ppm; HRMS (ESI, m/z): 609.0357 calcd for $C_{28}H_{21}Cl_3N_2O_6$ (M+Na) found: 609.0354. Analysis calcd for $C_{28}H_{21}Cl_3N_2O_6$: C, 57.21; H, 3.60; 4.77; Found C, 57.20; H, 3.59; N, 4.75.

Ethyl 4-(4-bromophenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11f: Light yellow colour solid, Yield 89%, Mp 172.5°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.49 (br s, 1H), 7.96-7.93 (m, 2H), 7.62-7.60 (m, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.20-7.18 (m, 3H), 4.73 (s, 3H), 4.22 (q, *J*=7.8 Hz, 2H), 2.03 (t, *J*=7.2 Hz, 2H), 1.97 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.31 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.3, 181.4, 167.0, 163.1, 162.9, 154.1, 144.0, 139.2, 135.2, 134.7, 131.4, 131.2, 130.3, 128.1, 127.5, 127.0, 126.3, 126.1, 122.2, 113.2, 101.4, 61.3, 32.2, 29.6, 15.2, 14.4, 13.1 ppm; HRMS (ESI, m/z): 585.0637 calcd for $C_{28}H_{23}BrN_2O_6$ (M+Na) found: 585.0634. Analysis calcd for $C_{28}H_{23}BrN_2O_6$: C, 59.69; H, 4.11; N, 4.97; Found C, 59.67; H, 4.10; N, 4.95.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-p-tolyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 11g: Light yellow colour solid, Yield 90%, M.p. 175.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.65 (br s, 1H), 12.52 (br s, 1H), 7.93-7.91 (m, 2H), 7.60-7.58 (m, 2H), 7.11 (d, *J*=8.0 Hz, 2H), 7.06 (d, *J*=8.0 Hz, 2H), 7.06 (d, *J*=7.8 Hz, 2H), 4.20 (q, *J*=7.8 Hz, 2H), 2.34 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.4, 167.2, 163.5, 162.3, 154.2, 139.4, 139.1, 135.4, 135.0, 134.9, 137.8, 130.8, 128.9, 126.8, 126.7, 125.5, 121.9, 113.5, 101.5, 61.7, 37.6, 29.9, 21.3, 15.1, 14.3, 12.9 ppm; HRMS (ESI, m/z): 521.1683 calcd for $C_{24}H_{18}N_2O_4$ (M+Na) found: 521.1682. Analysis calcd for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62; Found C, 69.87; H, 5.26; N, 5.62.

Ethyl 4-(2,4-dimethylphenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11h: Light yellow colour solid, Yield 88%, M.p. 163.9°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.56 (br s, 1H), 12.60 (br s, 1H), 7.94-7.90 (m, H), 7.59-7.57 (m, H), 6.99-6.98 (m, 2H), 6.92 (m, 1H), 4.74 (s,1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.04 (t, *J*=7.1, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.2, 163.7, 162.8, 154.1, 139.1, 136.7, 135.4, 135.0, 134.9, 131.8, 130.9, 130.7, 128.8, 126.8, 125.9, 121.9, 113.4, 101.4, 61.7, 35.0, 29.9, 21.6, 19.7, 16.2, 14.3, 13.1 ppm; HRMS (ESI, m/z): 535.1840 calcd for $C_{30}H_{28}N_2O_6$ (M+Na) found: 535.1837. Analysis calcd for $C_{30}H_{28}N_2O_6$: C, 70.30; H, 5.51; N, 5.47; Found C, 70.28; H, 5.50; N, 5.46.

Ethyl 4-(4-(dimethylamino)phenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11i: Light yellow colour solid, Yield 94%, M.p. 181.4°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.67 (br s, 1H), 12.59 (br s, 1H), 7.94-7.90 (m, 2H), 7.60-7.58 (m, 2H), 7.06 (d, *J*=2H), 6.64 (d, *J*=8.4 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.08 (s, 6H), 1.93 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.01 (t, *J*=7.2 Hz, 2H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.3, 181.6, 167.4, 163.7, 162.5, 154.1, 148.1, 139.4, 135.2, 135.0, 131.8, 130.8, 129.9, 126.8, 126.7, 121.9, 113.6, 112.3, 101.5, 61.7, 41.3, 41.2, 37.5, 29.9, 15.1, 14.3, 13.0 ppm; HRMS (ESI, m/z): 550.1954 calcd for $C_{30}H_{29}N_3O_6$ (M+Na) found: 550.1953. Analysis calcd for $C_{30}H_{29}N_3O_6$: C, 68.30; H, 5.54; N, 7.96; Found C, 68.28; H, 5.52; N, 7.95.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 11j: Light yellow colour solid, Yield 82%, M.p. 173.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 16.57 (br s, 1H), 12.60 (br s, 1H), 7.92-7.89 (m, 2H), 7.60-7.58 (m, 2H), 7.06 (d, *J*=8.2 Hz, 2H), 6.68 (d, *J*=8.2 Hz, 2H), 5.35 (br s, 1H), 4.74 (s, 1H), 4.20 (t, *J*=7.8 Hz, 2H), 2.04 (t, *J*=7.2 Hz, 2H), 2.01 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184., 181.5, 167.5, 163.5, 162.6, 155.5, 154.5, 139.1, 135.0, 134.9, 134.8, 131.8, 130.4, 126.8, 126.5, 121.9, 115.8, 113.4, 101.4, 61.7, 37.5, 29.9, 15.1, 14.3, 13.0 ppm; HRMS (ESI, m/z): 523.1481calcd for $C_{24}H_{18}N_2O_4$ (M+Na) found: 523.1483. Analysis calcd for $C_{28}H_{24}N_2O_7$: C, 67.19; H, 4.83; N, 5.60; Found C, 67.17; H, 4.81; N, 5.57.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11k: Light yellow colour solid, Yield 87%, M.p. 179.1°C, IR (KBr) υ_{max} 3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.75 (br s, 1H), 12.57 (br s, 1H), 7.94-7.92 (m, 2H), 7.60-7.58 (m, 2H), 7.12 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.74 (s, 1H), 4.20 (t, *J*=7.8 Hz, 2H), 3.83 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.5, 163.7, 162.8, 157.6, 154.1, 139.1, 135.0, 134.9, 134.6, 131.8, 130.6, 126.8, 126.7, 121.9, 114.2, 113.4, 101.5, 61.6, 55.9, 37.5, 29.9, 15.3, 14.4, 13.0 ppm; HRMS (ESI, m/z): 537.1632 calcd for $C_{29}H_{26}N_2O_7$ (M+Na) found: 537.1630. Analysis calcd for $C_{29}H_{26}N_2O_7$: C, 67.70; H, 5.09; N, 5.44; Found C, 67.68; H, 5.07; N, 5.43.

Ethyl-4-(3,4-dimethoxyphenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 11l: Light yellow colour solid, Yield 95%, M.p. 176.5°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$ 16.73 (br s, 1H), 12.53 (br s, 1H), 7.95-7.93 (m, 2H), 7.59-7.57 (m, 2H), 6.88 (s, 1H), 6.76 (d, *J*=6.8 Hz, 1H), 6.68 (d, *J*=6.8 Hz, 1H), 4.74 (s, 1H), 4.23 (q, *J*=7.8 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.04 - 2.02 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.8, 167.5, 163.4, 162.8, 154.3, 149.8, 146.8, 139.1, 135.0, 134.8, 131.8, 130.8, 126.7, 126.5, 122.9, 121.3, 113.4, 112.3, 101.5, 61.7, 56.3, 56.2, 37.8, 29.9, 15.1, 14.2, 13.2 ppm; HRMS (ESI, m/z): 567.1743 calcd for $C_{30}H_{28}N_2O_8$ (M+Na) found: 567.1740. Analysis calcd for $C_{30}H_{28}N_2O_8$: C, 66.17; H, 5.18; N, 5.14; Found C, 66.16; H, 5.17; N, 5.12.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carboxylate 11m: Yellow colour solid, Yield 88%, M.p. 179.3°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.5 (br s, 1H), 12.51 (br s, 1H), 7.95-7.93 (m, 2H), 7.59-7.57 (m, 2H), 7.51 (d, *J*=7.6 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.9, 167.2, 163.7, 162.5, 154.1, 148.5, 144.9, 139.2, 135.0, 134.1, 131.7, 130.8, 129.8, 126.8, 123.8, 121.9, 113.4, 101.4, 14.2, 37.4, 29.9, 15.1, 14.2, 13.3 ppm; HRMS (ESI, m/z): 552.1383 calcd for $C_{28}H_{23}N_3O_8$ (M+Na) found: 552.1380. Analysis

calcd for $C_{28}H_{23}N_3O_8$: C, 63.51; H, 4.38; N, 7.94; Found C, 63.50; H, 4.36; N, 7.92.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11n: Yellow colour solid, Yield 86%, M.p. 177.4°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H=NMR (400 MHz, $CDCl_3$), δ=16.77 (br s, 1H), 12.62 (br s, 1H), 8.12 (s, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 7.92 (d, *J*=7.8 Hz, 2H), 7.62 – 7.60 (m, 3H), 7.58 (t, *J*=7.8 Hz,1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=.7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.1, 181.5, 167.2, 163.7, 162.7, 154.1, 147.8, 147.3, 139.1, 135.0, 134.9, 133.3, 131.8, 130.8, 126.9, 126.7, 121.8, 121.5, 120.8, 120.6, 120.5, 113.4, 101.4, 61.8, 36.5, 30.3, 16.5, 14.2, 13.3 ppm; HRMS (ESI, m/z): 552.1383 calcd for $C_{28}H_{23}N_3O_8$ (M+Na) found: 552.1380. Analysis calcd for $C_{28}H_{23}N_3O_8$: C, 63.51; H, 4.38; N, 7.94; Found C, 63.50; H, 4.36; N, 7.91.

Ethyl 4-(furan-2-yl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11o: Yellow colour solid, Yield 87%, M.p. 177.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.7 (br s, 1H), 12.59 (br s, 1H), 7.92-7.90 (m, 1H), 7.60-7.58 (m, 2H), 7.58 (d, *J*=8.0 Hz, 2H), 6.40 (d, *J*=8.0 Hz, 1H), 6.08 (d, *J*=8.0 Hz, 1H), 4.97 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.98 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.9, 167.2, 163.7, 162.8, 154.2, 152.5, 142.2, 139.2,135.0, 134.9, 131.8, 130.8, 126.8, 126.5, 121.9, 113.4, 110.5, 106.7, 101.4, 61.7, 29.7, 15.3, 14.3, 13.0 ppm; HRMS (ESI, m/z): 497.1319 calcd for $C_{26}H_{22}N_2O_7$ (M+Na) found: 497.1317. Analysis calcd for $C_{26}H_{22}N_2O_7$: C, 65.82; H, 4.67; N, 5.90; Found C, 65.80; H, 4.64; N, 5.87.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-(thiophen-2-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11p: Light yellow colour solid, Yield 93%, M.p. 179.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.7 (br s, 1H), 12.58 (br s, 1H), 7.92-7.90 (m, 1H), 7.59-7.57 (m, 2H), 7.40 (d, *J*=8.0 Hz, 2H), 6.93-6.91 (m, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.98 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.4, 167.4, 163.7, 162.8, 154.1, 139.4, 139.1, 135.0, 134.9, 131.8, 130.6, 127.0, 126.8, 126.7, 126.6, 125.5, 121.9, 113.4, 101.4, 61.7, 29.9, 29.3, 15.1, 14.2, 13.1 ppm; HRMS (ESI, m/z): 513.1096 calcd for $C_{26}H_{22}N_2O_6S$ (M+Na) found: 513.1093. Analysis calcd for $C_{26}H_{22}N_2O_6S$: C, 63.66; H, 4.52; N, 5.71; S, 6.54; Found C, 63.64; H, 4.50; N, 5.69; S, 6.52.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-(pyridin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11q: Light yellow colour solid, Yield 87%, M.p. 184.4°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.52 (br s, 1H), 12.62 (br s, 1H), 7.92-7.90 (m, 2H), 7.65 (d, *J*=8.2 Hz, 2H), 7.60-7.58 (m, 1H), 7.25 (m, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.0, 181.5, 167.0, 163.6, 162.7, 154.3, 150.1, 147.3, 139.1, 135.0, 134.9, 134.3, 132.6, 131.8, 130.6, 126.8, 126.7, 123.0, 121.7, 113.5, 101.5, 61.7, 37.5, 29.7, 15.2, 14.2, 13.1 ppm; HRMS (ESI, m/z): 508.1485 calcd for $C_{27}H_{23}N_3O_6$ (M+Na) found: 508.1480. Analysis calcd for $C_{27}H_{23}N_3O_6$: C, 72.35; H, 4.55; N, 7.03; Found C, 72.33; H, 4.54; N, 7.0.

Ethyl 6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11r: Yellow colour solid, Yield 90%, M.p. 175.1°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.61 (br s, 1H), 12.62 (br s, 1H), 7.92 -7.90 (m, 2H), 7.60 - 7.58 (m, 2H), 7.52 (d, *J*=8.0 Hz, 2H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7. Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.5, 167.2, 163.7, 162.8, 154.1, 145.6, 139.1, 135.0, 134.9, 131.8, 130.8, 129.3, 128.0, 126.8, 126.7, 125.0, 124.1, 121.9, 113.4, 101.4, 61.7, 37.5, 29.9, 15.1, 14.5, 13.1 ppm; HRMS (ESI, m/z): 575.1400 calcd for $C_{29}H_{23}F_3N_2O_6$ (M+Na) found: 575.1397. Analysis calcd for $C_{29}H_{23}F_3N_2O_6$: C, 63.04; H, 4.20; N, 5.07; Found C, 63.02; H, 4.19; N, 5.05.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-6-(2-(3-hydroxy-1,4-dioxo-1,4-dihydro naphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11s: Yellow colour solid, Yield 91%, Mp 183.5°C, IR (KBr), υ_{max}=3120, 3003, 2984, 1790, 1638, 1461, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.77 (br s, 1H), 12.62 (br s, 1H), 7.92-7.90 (m, 2H), 7.60 - 7.58 (m, 2H), 7.43 (s, 1H), 7.40 (d, *J*=8.2 Hz, 1H), 7.16 (d, *J*=8.0 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 181.6, 167.2, 163.8, 162.7, 154.1, 139.1, 138.7, 135.0, 134.8, 132.6, 131.8, 127.3, 126.8, 125.9, 123.40, 123.41, 120.9, 113.4, 101.5, 61.6, 37.9, 29.7, 15.1, 14.2, 13.1 ppm; HRMS (ESI, m/z): 643.1274 calcd for $C_{30}H_{22}F_6N_2O_6$ (M+Na) found: 643.1272. Analysis calcd for $C_{30}H_{22}F_6N_2O_6$: C, 72.35; H, 4.55; N, 7.03; Found C, 72.33; H, 4.54; N, 7.01.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-6-(2-(3-hydroxy-8-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11t: Yellow colour solid, Yield 87%, M.p. 182.2°C, IR (KBr) υ_{max} 3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.70 (br s, 1H), 12.58 (br s, 1H), 8.12 (t, *J*=7.8 Hz, 1H), 7.46 -7.44 (m, 2H), 7.43 (s, 1H), 7.19 (d, *J*=8.0 Hz, 1H), 7.16 (d, *J*=7.4 Hz, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.81 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=183.0, 181.5, 167, 168.8, 162.6, 160.0, 154.3, 139.4, 138.6, 136.0, 134.2, 132.9, 132.6, 127.5, 125.3, 123.4, 121.9, 120.9, 119.1, 117.9, 113.4, 101.4, 61.7, 55.8, 37.9, 29.8, 15.4, 14.0, 13.2 ppm; HRMS (ESI, m/z): 673.1385 calcd for $C_{31}H_{24}F_6N_2O_7$ (M+Na) found: 673.1383. Analysis calcd for $C_{31}H_{24}F_6N_2O_7$: C, 57.24; H, 3.72; N, 4.31; Found, C, 57.24; H, 3.72; N, 4.31.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-6-(2-(3-hydroxy-6,8-dimethoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11u: Yellow colour solid, Yield 91%, M.p. 180.4°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ=16.70 (br s, 1H), 12.58 (br s, 1H), 7.43-7.41 (m, 2H), 7.19 (s, 1H), 7.16 (d, *J*=1H), 7.07 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ=183.0, 181.6, 167.3, 165.1, 163.7, 162.8, 162.6, 154.1, 139.1, 138.6, 132.6, 132.4, 127.3, 125.3, 123.3, 121.9, 120.8, 115.3, 113.2, 106.4, 103.5, 101.4, 61.7, 55.93, 55.92, 37.9, 29.9, 15.2, 14.2, 13.2 ppm; HRMS (ESI, m/z): 703.1486 calcd for $C_{32}H_{26}F_6N_2O_8$ (M+Na) found: 703.1483. Analysis calcd for $C_{32}H_{26}F_6N_2O_8$: C, 56.48; H, 3.85; N, 4.12; Found C, 56.48; H, 3.85; N, 4.12.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-6-(2-(3-hydroxy-5,7,8-trimethoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11v: Colour, Yield 82%, M.p. 188.8°C, IR (KBr), υ_{max}=3122, 3010, 2988, 1793, 1644, 1445, 1381, 1203, 1094, 815, 744, 731, 640 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.68 (br s, 1H), 12.62 (br s, 1H), 7.43-7.42 (m, 2H), 7.16 (d, *J*=7.2 Hz, 1H), 6.94 (s, 1H), 4.74 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ=184.4, 183.0, 167.5, 163.7, 162.8, 157.4, 154.9, 154.1, 147.5, 139.1, 138.6, 132.5, 128.9, 127.3, 125.3, 123.8, 123.5, 123.2, 121.6, 120.9, 113.4, 107.9, 101.4, 61.7, 56.3, 55.8, 37.8, 29.9, 15.1, 14.2, 13.1 ppm; HRMS (ESI, m/z): 733.1597calcd for $C_{33}H_{28}F_6N_2O_9$ (M+Na) found: 733.1595. Analysis calcd for $C_{33}H_{28}F_6N_2O_9$: C, 55.78; H, 3.97; N, 3.94; Found C,

55.76; H, 3.95; N, 3.93.

Ethyl 4-(3,4-bis(trifluoromethyl)phenyl)-3-methyl-6-(2-(3,5,7,8-tetrahydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)ethyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carboxylate 11x: Colour, Yield 80%, M.p. 176.5°C, IR (KBr), υ_{max}=3214, 3114, 3004, 2982, 1794, 1642, 1456, 1394, 1324, 1224, 1076, 813, 735, 721, 648 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$), δ=16.53 (br s, 1H), 12.45 (br s, 1H), 10.43 (br s, 1H), 10.37 (br s, 2H), 7.44-7.42 (m, 2H), 7.28 (d, *J*=7.2 Hz, 1H), 7.04 (s, 1H), 4.72 (s, 1H), 4.20 (q, *J*=7.8 Hz, 2H), 3.83 (s, 6H), 3.82 (s, 3H), 2.04 (t, *J*=7.2 Hz, 2H), 2.02 (t, *J*=7.2 Hz, 2H), 1.93 (s, 3H), 1.29 (t, *J*=7.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$), δ=184.2, 183.1, 166.4, 163.3, 162.5, 157.8, 156.2, 154.7, 146.3, 138.9, 138.4, 133.2, 129.1, 128.3, 125.0, 123.8, 123.4, 123.1, 120.9, 120.6, 113.2, 107.5, 101.2, 61.8, 37.6, 29.4, 15.0, 14.2, 13.1 ppm; HRMS (ESI, m/z): 691.1127 calcd for $C_{30}H_{22}F_6N_2O_9$ (M+Na) found: 691.1123. Analysis calcd for $C_{30}H_{22}F_6N_2O_9$: C, 55.78; H, 3.97; N, 3.94; Found C, 55.76; H, 3.95; N, 3.93.

BIOLOGICAL EVALUATION

Antimicrobial activity

The newly synthesized and well characterized compounds (11a-x) were screened for *in vitro* antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus epidermidis* and *Proteus vulgaris* and antifungal activity against *Aspergillus flavus*, *Monascus purpureus*, *Aspergillus niger*, *Penicillium citrinum*, *Candida albicans* using agar well diffusion assay and zones of inhibition of the test compounds were expressed in mm. For biological tests 23 of three types of compounds are selected.

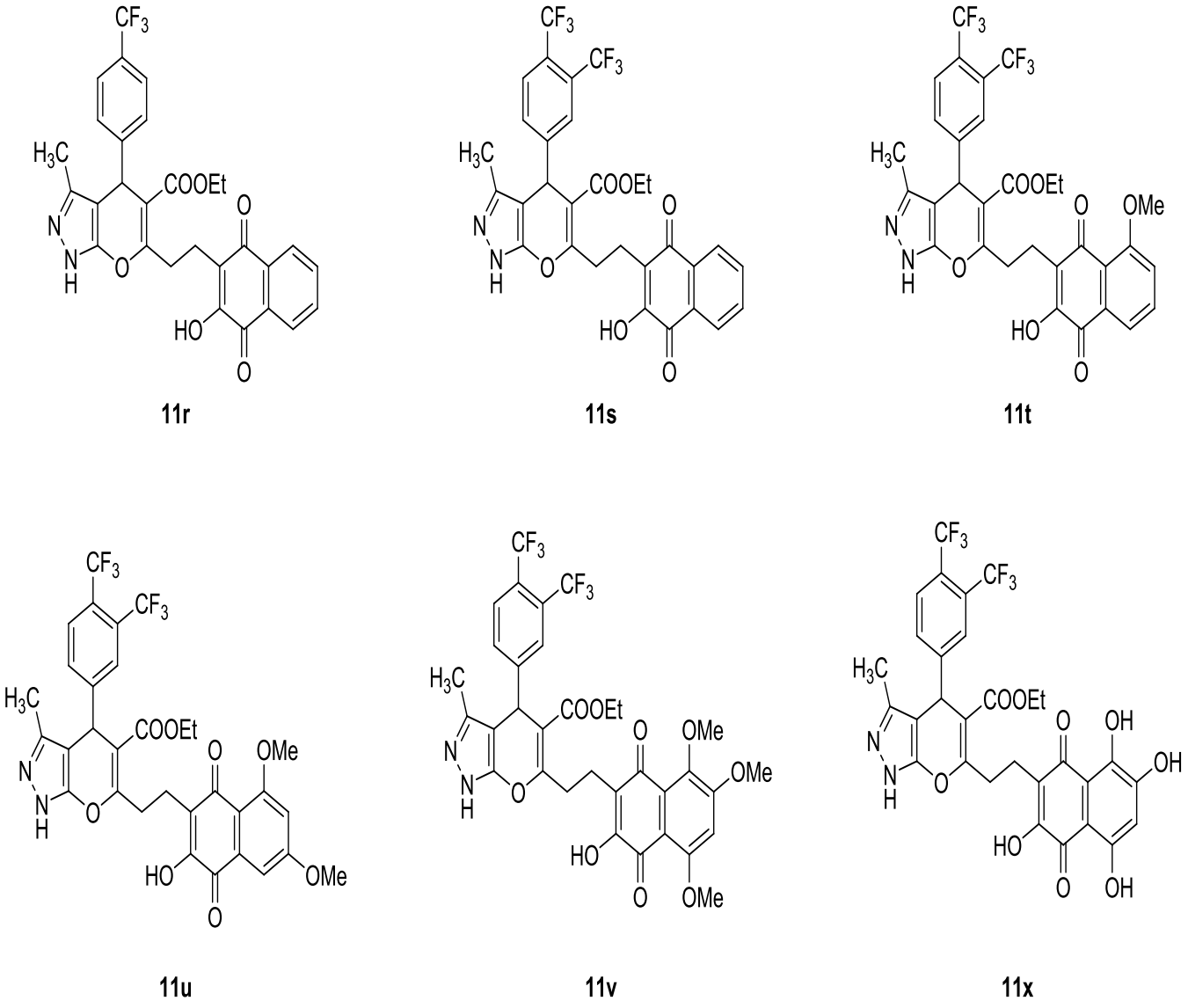


Figure 2: Synthesis of SAR directed a combinatorial library of highly biologically active fluorinated pyranopyrazole-napthaquinone hybrids for anti-microbial activity

In the first phase, antibacterial activity of 17 compounds was evaluated in *in vitro* against of four microbial stains. The results of zone inhibition of compounds 11a-x against bacterial stain are gathered in Table 1. Studies reveals that dichloro, trichloro, trifluoromethyl group substituted compounds, 11d, 11e, 11r shows significant microbial activity (entry 4, 5, 18). The next batch of six PPN hybrids (11s-x) substituted was kept intact and changes were made in ring B. Antibacterial evaluation revealed that PPN hybrid 11x (Entry 23) which has OMe group on aromatic ring B and CF3 of ring A displays better activity compared with others against of bacterial stain with zone of inhibition of 12, 11, 13, 11 and 12 nm respectively.

Table 1: Zone of inhibition (mm)[a] of compounds 11a-x against tested bacterial strains

Entry	Compound	Bacterial strains			
		Bacillus subtilis	***Escherichia coli***	***Staphylococcus epidermidis***	***Proteus vulgaris***
1.	11a	6	5	8	10
2.	11b	5	6	9	10
3.	11c	6	7	11	9
4.	11d	4	5	9	8
5.	11e	4	6	8	10
6.	11f	3	8	12	11
7.	11g	8	7	10	10
8.	11h	7	7	10	9
9.	11i	4	8	11	8
10.	11j	7	7	12	11
11.	11k	6	7	10	12
12.	11l	7	8	10	11
13.	11m	7	5	8	9
14.	11n	4	6	10	9
15.	11o	5	6	8	10
16.	11p	9	6	9	10
17.	11q	8	8	10	11
18.	**11r**	**10**	**10**	**14**	**14**
19.	**11s**	**10**	**11**	**13**	**15**
20.	**11t**	**11**	**13**	**15**	**14**
21.	**11u**	**12**	**13**	**17**	**15**
22.	**11v**	**12**	**14**	**14**	**16**
23.	**11x**	**13**	**17**	**16**	**15**
24.	Standard	24	27	22	26

Ciprofloxacin was used as standard. [a] 100 µg/mL of compound in each well

Antifungal activity

The antifungal activity of tested compounds (11a-x) were compared with ketoconazole (standard) and the results are tabulated in Table 2 infer that compound 11v was found to be interesting molecule with good antifungal activity against *A. flavus*, *M. purpureus*, *A. niger*, *P. citrinum* and *C. albicans*. In the first phase, antibacterial activity of 17 compounds was evaluated in *in vitro* against of five microbial stains. The results of zone inhibition of compounds 11a-x against fungal stains are gathered in Table 2. Studies reveals that dichloro, trichloro, trifluoromethyl group substituted compounds11d, 11e, 11r shows significant microbial activity (entry 4, 5, 18). The next batch of six PPN hybrids (11s-x) substituted was kept intact and changes were made in ring B. Antibacterial evaluation revealed that PPN hybrid 11x (Entry 23) which has OMe group on aromatic ring B and CF3 of ring A displays better activity compared with others against of bacterial stain with zone of inhibition of 16, 14, 17, 14 and 13 nm respectively.

Table 2: Zone of inhibition (mm)[a] of compounds 11a-x against tested fungal strains

Entry	Compound	***Aspergillus flavus***	***Monascus purpureus***	***Aspergillus niger***	***Penicillium citrinum***	***Candida albicans***
1	11a	9	4	8	3	3
2	11b	8	3	8	4	4
3	11c	8	4	7	4	3
4	11d	12	6	13	7	11
5	11e	12	6	12	6	11
6	11f	10	6	8	7	8
7	11g	8	4	7	3	6
8	11h	9	3	6	2	7
9	11i	7	2	7	4	7
10	11j	6	4	5	3	6
11	11k	10	7	10	7	11
12	11l	10	7	10	8	11
13	11m	7	3	7	3	5
14	11n	8	4	9	4	7
15	11o	8	5	6	6	5
16	11p	9	4	9	7	7
17	11q	9	6	8	5	9
18	**11r**	12	11	12	9	11
19	**11s**	14	10	14	13	11
20	**11t**	11	9	12	9	10
21	**11u**	11	9	10	12	10
22	**11v**	12	11	13	11	12
23	**11x**	16	14	17	14	13
21	Standard	21	18	23	16	19

Antiproliferative activity

In the first phase, antiproliferative activity of seventeen pyranopyrazole-napthaquinone hybrids (11a-r, Figure 2) was evaluated *in vitro* against a panel of four human cancer cell lines, namely DLD1-(colorectal adenocarcinoma), DU145 (prostate carcinoma), A549 (lung carcinoma), FaDu (hypopharyngeal carcinoma) and the results for inhibitory concentration (IC_{50}) values are gathered in Table 3. The studies reveal that methoxy group substituted C3 dihydrofuran substituted hybrids 11k and 11r showed significant cytotoxic activity in comparison with other derivatives in all the four cell lines (entry 11 & 18, Table 3). For the next batch of six PPN hybrids (11s-x) substitution was kept intact and changes were made

in ring A and B. Antiproliferative evaluation of 11a-t revealed that PPN hybrid 11t (entry 19) which has methoxy group at aromatic ring B and triflouro methyl group at aromatic ring A displays better activity compared to others. For next batch of hybrids 11r-x changes were made ring A and in ring B with OMe, CF_3 groups. Anti-proliferative evaluation of 11r-x revealed that 11v which has two methoxy, two CF_3 groups displays better activity compared to others (entry 23). In summary *in vitro* evaluation revealed that PPN hybrids 11v is the most potent molecule within the batch of 11r-x. In order to determine the cytotoxic effects, all the twenty three compounds were subjected to *in vitro* cytotoxicity assay using 3-[4,5-Dimethylthiazol-2-yl]-2,5-Diphenyltetrazolium Bromide (MTT) reduction test with the panel of four cancer cell lines for 48 h. All the compounds exhibited minimal cytotoxicity on 'Human Peripheral Blood Mononuclear Cell' (hPBMC), which indicates that PNN hybrids 11a-x are selectively toxic towards cancer cell lines.

Table 3: *In vitro* antiproliferative activity of pyranopyrazole -napthaquinone hybrids (11a-x) against DLD1, Du145, A549, FaDu human cancer cells by MMT assay expressed in IC_{50}(µM)[a]

Entry	Compounds	DLD1[b]	Du145[c]	A549[d]	FaDu[e]
1	11a	42 ± 0.91	> 100	> 100	> 100
2	11b	41 ± 1.85	> 100	> 100	> 100
3	11c	43 ± 0.52	> 100	> 100	> 100
4	11d	40 ± 1.32	> 100	> 100	> 100
5	11e	29 ± 2.5	> 100	41 ± 1.72	> 100
6	11f	25 ± 1.65	47 ± 0.75	49 ± 2.5	> 100
7	11g	31 ± 0.80	> 100	> 100	> 100
8	11h	36 ± 3.63	> 100	> 100	55 ± 1.6
9	11i	32 ± 4.78	47 ± 0.45	> 100	> 100
10	11j	30 ± 0.62	41 ± 1.53	> 100	> 100
11	11k	29 ± 1.65	37 ± 0.76	34 ± 0.5	35 ± 0.65
12	11l	37 ± 0.20	38 ± 1.03	44 ± 0.25	37 ± 0.06
13	11m	50 ± 9.83	45 ± 0.04	45 ± 0.04	44 ± 0.15
14	11n	47 ± 2.8	53 ± 0.4	58 ± 0.05	42 ± 0.17
15	11o	28 ± 0.15	56 ± 0.71	45± 0.75	45 ± 1.55
16	11p	29 ± 0.52	34 ± 0.22	39 ±0.84	35 ± 0.96
17	11q	19 ± 0.24	38 ± 0.4	28 ± 0.52	24 ± 0.88
18	**11r**	**17 ± 0.50**	**29 ± 0.1**	**25 ± 0.28**	**18 ± 0.78**
19	**11s**	**16 ± 0.10**	**27 ± 0.83**	**21 ± 0.83**	**16 ± 1.31**
20	**11t**	**16 ± 0.13**	**27 ± 0.11**	**22 ± 0.15**	**16 ± 0.73**
21	**11u**	**16 ± 1.25**	**27 ± 0.32**	**22 ± 0.03**	**15 ± 1.25**
22	**11v**	**16 ± 0.15**	**26 ± 0.04**	**21 ± 0.75**	**15 ± 0.96**
23	**11x**	**15 ± 0.18**	**25 ± 0.95**	**21 ± 0.17**	**14 ± 0.24**
18	**Tamoxifen**	11 ± 0.65	18 ± 1.70	17 ± 1.06	5.39 ± 0.34

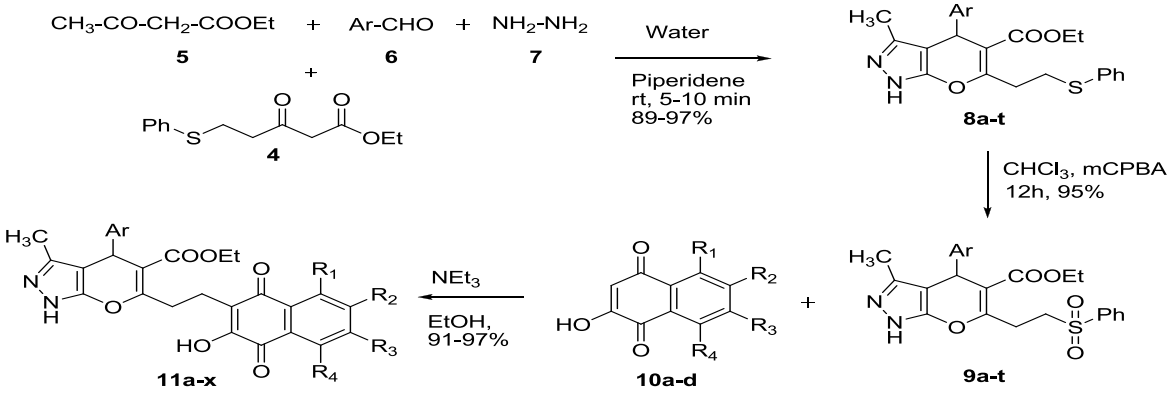
[a]Results are the average of three independent experiments; [b]DLD1-(colorectal adenocarcinoma); [c]DU145 (prostate carcinoma), [d]A549 (lung carcinoma), [e]FaDu (hypopharyngeal carcinoma)

RESULTS AND DISCUSSIONS

Starting material salfonyl β-keto ester 4 synthesized by employing Blaise reaction. According to the Blaise reaction protocol acrylonitrile 1, thiophenol 2, ethylbromo acetate 3 treated with zinc and Chlorotrimethylsilane (TMSCl) provided phenylthio β-keto ester (Scheme 1) [18,19].

Scheme 1: Synthesis of phenylthio β-keto ester by Blaise reaction

In the reaction protocol when equimolar amounts mixture of ethylacetoacetate, aromatic aldehyde, hydrazine, sulfonyl β-ketoester and piperidene as a catalyst were refluxed in EtOH solvent provide sulfonated pyranopyrazoles 8a-t. Sulfur was oxidized by treating with mCPBA provides sulfonated pyranopyrazoles 9a-t, in which SO_2 can easily replace with electron rich Napthaquinone derivatives 10a-d provided pyranopyrazole-naphthoquinone hybrid 11a-x (Scheme 2).



Scheme 2: Synthesis of antimicrobial active pyranopyrazole and napthaquinone hybrids 11a-x

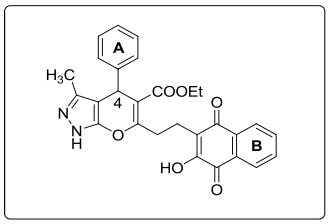


Figure 3: Structure of pyranopyrazole and napthaquinone hybrid

^{1}H-NMR spectra of 11a shows δ=4.51 ppm for pyranone ring C4 proton, δ=2.2 and 2.0 two triplets for two CH_2 groups between two rings and two broad singlets appears at δ=16.65, 12.51 ppm for OH and NH groups. ^{13}C-NMR shows 26 signals unequivocally. Finally structure can be confirmed by the HRMS spectra where (M+Na) peak appear at 507.1526. Similarly, compounds 11ax was synthesized and characterized (Figure 3). Newly prepared Pyranopyrazole-Napthaquinone hybrid derivatives 11a-x was subjected to *in-vitro* antibacterial activity against *B. subtilis*, *E. coli*, *S. epidermidis* and *P. vulgaris* bacterial stains and antifungal activity against *A. flavus*, *M. purpureus*, *A. niger*, *P. citrinum* and *C. albicans* and anticancer activity against of DLD1-(colorectal adenocarcinoma), DU145 (prostate carcinoma), A549 (lung carcinoma), FaDu (hypopharyngeal carcinoma) human cancer cell lines. Out of which, the 11r emerged as the most promising lead compound open for further structure activity relationship (SAR) studies (Tables 1-3). Two domains in 11r namely, the aromatic ring (ring A, Figure 2) of pyranopyrazole and aromatic ring (of ring B, Figure 2) on napthaquinone were agreeable for alteration with different substituents while keeping rest of the molecule intact. Spectral (IR, ^{1}H-NMR, ^{13}C-NMR and DEPT) and analytical (ESI-MS HRMS) data of the all the derivatives 11b-x agreed well with the assigned structures. We gathered structures of all the PPN hybrids11a-x along with the time taken for the substitution reaction and yield of the product in Figure 4 to provide overall picture of the substitution pattern and to discern SAR results.

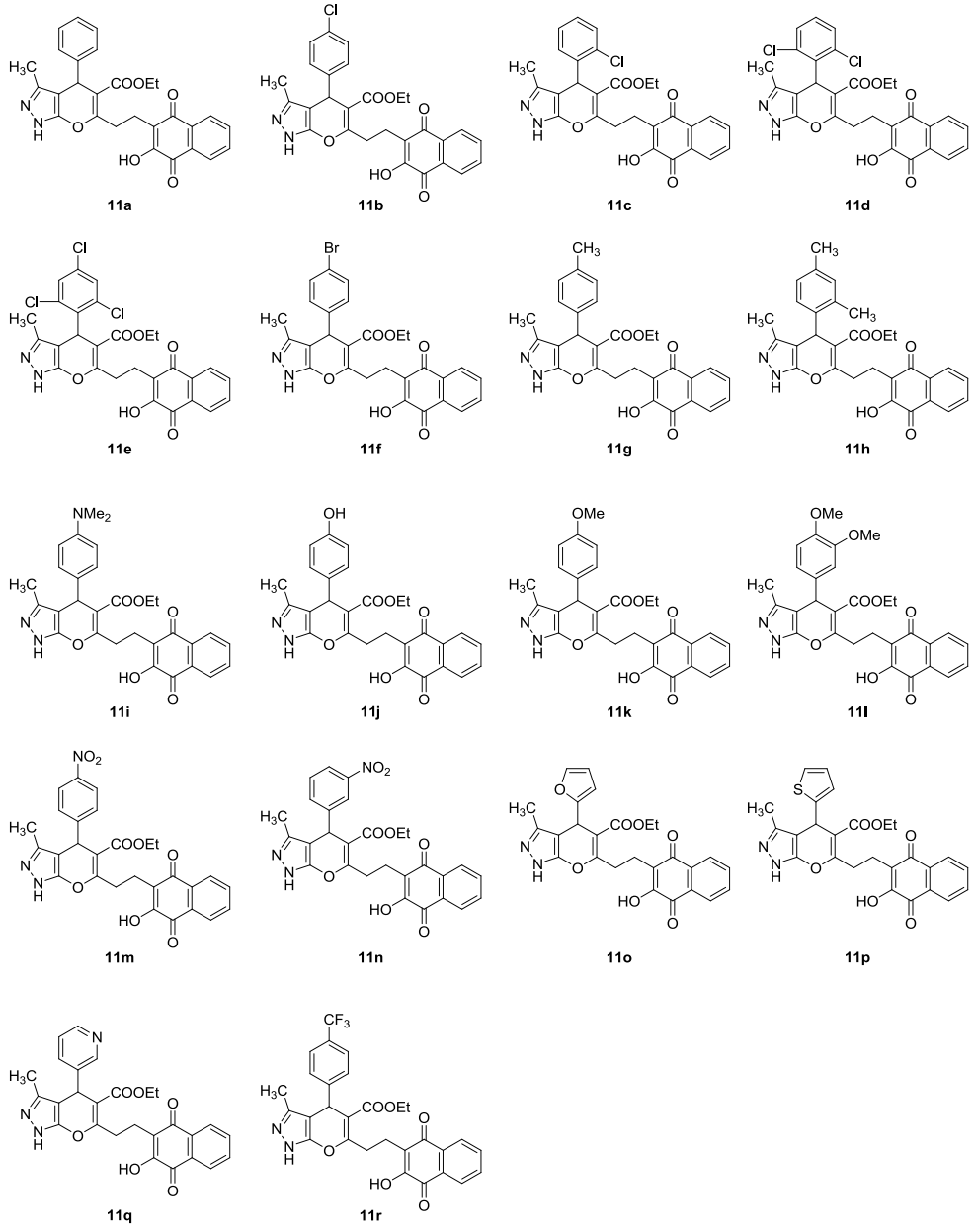


Figure 4: List of compounds screened for the first phase

CONCLUSION

In summary, we have synthesized a combinatorial library of pyranopyrazole-naphthaquinone hybrids among the novel series pyranopyrazole napthaquinone hybrids (11a-x) compound 11r-x (*B. subtilis*, *E. coli*, *S. epidermidis* and *P. vulgaris*) potent for antibacterial activity and similarly compound 11r-x (*A. flavus*, *M. purpureus*, *A. niger*, *P. citrinum* and *C. albicans*) exhibit good antifungal activity. Evaluated their antiproliferative activity against DLD1 (colorectal adenocarcinoma), DU145 (prostate carcinoma), A549 (lung carcinoma), FaDu (hypopharyngeal carcinoma). Among these pyranopyrazole-naphthaquinone hybrids, compounds having two tri fluoro methyl groups and three methoxy groups displayed the most potent anti-proliferative activity against the four-cell lines uniformly. Toxicity studies revealed that the PPN hybrids (11a-x) are specifically targeting the cancer cell lines. Thus we have discovered 11r, 11s, 11t, 11u, 11v were acts as the most potential anti-cancer molecules.

ACKNOWLEDGEMENT

VST thanks to IICT Hyderabad, University of Hyderabad for recording NMR and Mass Spectra, Department of Microbiology, Sri Venkateshwara University for biological evolution of samples.

REFERENCES

[1] S.C. Kuo, S.C. Huang, L.J. Nakamura, *J. Med. Chem*., **1984**, 27, 539.
[2] L.J. Huang, M.J. Hour, C.M. Teng, S.C. Kuo, *Chem. Pharm. Bull*., **1992**, 40, 2547.
[3] S. Schwikkard, F. Van Heerden, *Nat. Prod. Rep*., **2002**, 19, 625.
[4] O.F.G. Manlia, C.L. Zani, T. Josealdo, R.F. Lueiano, C.A. Fabiane, B.O. Alalde, S. Raslan, S. Sergia, C. Egler, *Bioorg. Med. Chem. Lett.*, **1997**, 7, 2043.
[5] K. Likhitwitayawuid, R. Kaewamatawong, N. Ruangrungsi, *Plarita Med*., **1998**, 64.
[6] E.A. Sausville, R.W. Stein, J. Peisach, S.B. Horwitz, *Biochemistry*., **1978**, 17, 2746.
[7] R.M. Burger, *Chem. Rev*., **1998**, 98, 1153.
[8] Y. Zou, N.E. Fahmi, C. Vialas, Miller, G.M. Hecht, *J. Am. Chem. Soc*., **2006**, 124, 9476.
[9] B. Meunier, *Acc. Chem. Res*., **2008**, 41, 69.
[10] V.S. Tangeti, G.V. Siva Prasad, J. Panda, K.R. Varma, *Synth. Communi* **2016**, 46, 878.
[11] H.S.P. Rao, V.S. Tangeti, *J. Chem. Sci.*, **2013**, 125, 777.
[12] H.S.P. Rao, V.S. Tangeti, A. Laxminarayana, *Res. Chem. Intermed*., **2016**, 42, 7285.
[13] V.S. Tangeti, K.R. Varma, G.V. Siva Prasad, K.V.V.V. Satyanarayana, *Synth. Commun.*, **2016**, 46, 613.
[14] H.S.P. Rao, V.S. Tangeti, *Lett. Org. Chem*., **2012**, 9, 218.
[15] H.S.P. Rao, V.S. Tangeti, *Proceedings of National Academy of Sciences-India sec-a*., **2015**, 85, 41.
[16] S.T. Nishith, H.S.P. Rao, V.S. Tangeti, R. Krishna, *Acta. Cryst*., **2013**, E6, o284.
[17] V.S. Tangeti, D. Vasundhara, K.V.V.V. Satyanarayana, K.S.P. Kumar, *Asian J. Chem*., **2017**, 29, 527.
[18] H.S.P. Rao, S.K. Rafi, K. Padmavathy, *Lett. Org. Chem*., **2008**, 5, 527.
[19] H.S.P. Rao, N. Muthanna, *Synlett*., **2016**, 27, 2014.