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Synthesis and Biological Evaluation of 2-Amino-4*H*-pyran-3,4,5-tricarboxylate Salt Derivatives

Ali Akbari*, Zabihollah Azami-Sardooei†, and Asghar Hosseini-Nia‡
Department of Chemistry, Faculty of Science, University of Jiroft, Jiroft, P.O. Box 8767161167, Iran
**E-mail: a.akbari@ujiroft.ac.ir*
†Department of Corp Protection, Faculty of Agriculture, University of Jiroft, Jiroft, P.O.Box 8767161167, Iran
‡Department of Plant Protection National Research Station of Ornamental Plants, Mahallat, P.O.Box 37815-137, Iran
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ABSTRACT. A novel and simple method for the synthesis of 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivative and the evaluation of their antibacterial activity against *Pseudomonas syringae*, *Xanthomonas citi* and *Pectobacterium carotovorum* are reported. The structure of the isolated compounds has been determined by means of $^{1}H/^{13}C$ NMR and FT-IR Spectroscopy. The reaction of alkyl isocyanides with acetylenic esters in the presence of dimethyl acetone-1,3-dicarboxylate in the present of $BF_3.SiO_2$ at ambient temperature. Some of the compound showed significant inhibition to growth of bacteria.

Key words: Biological evaluation, Antibacterial activity, 4*H*-Pyran-3,4,5-tricarboxylate, $BF_3.SiO_2$

INTRODUCTION

Homogeneous acidic catalysts such as H_2SO_4, HCl and BF_3 are commonly used for organic synthesis. However, the above-mentioned catalysts have several disadvantages because they are corrosive, toxic or volatile, and generate large amounts of waste. Silica supported boron trifluoride, $BF_3.SiO_2$, which is easy to prepare and shows unusually high Brønsted acidity which can be controlled by activation temperature, and exhibits considerable catalytic activity[1] enables better accessibility of the reactants to the active sites. $BF_3.SiO_2$ is a solid super acid and has surface species such as Al–OBF_2 and Si–OBF_2, and the ion pairs, Al–OBF_3^-–H^+ or Si–OBF_3^-–H^+.[2] The $BF_3.SiO_2$ is used in several organic transformations, such as in Claisen-Schmidt condensations,[3] in synthesis of 14-aryl or alkyl-14*H*-dibenzo[*a,j*]xanthenes,[4] 1,2,4,5-tetrasubstituted imidazoles,[5] in the polymerization of styrene,[6] the preparation of polyfunctionalized piperidin-4-ones,[7] α-amino phosphonates,[8] quinoxalines,[9] and 3,4-dihydropyrimidin-2(1*H*)-ones.[10]

4*H*-pyranes have recently attracted much attention as an important class of heterocyclic having useful biological and pharmacological properties, such as cytotoxic (anticancer),[11–13] neuroprotective,[14] HIV-inhibitory,[15] antimicrobial,[16, 17] antifungal,[18] and antioxidant activity.[19] Recently, one methods has been reported for the synthesis of pyran derivatives via a three-component condensation of alkylisocyanides with acetylenic esters and 1,3-diketones to synthesis of 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivatives.[20] We reported the synthesis of fused 2-amino-4*H*-pyrane derivatives from the reaction of alkylisocyanides with acetylenic esters and 1,3-diketones, in the presence of $BF_3.SiO_2$ in H_2O at room temperature. synthetic methodology for the synthesis of 4*H*-pyran as a part of green chemistry approach. H_2O is a naturally occurring, cheap, and non-toxic ecofriendly solvent. And biological evaluation antibacterial activity against *Pseudomonas syringae, Xanthomonas citi* and *Pectobacterium carotovorum* with improved in vitro therapeutic index. These heterocycles then screened for their antibacterial activity against X. campestris pvs, P. syringae and P. carotovorum using Tetracyclin as standard antibiotic. Interestingly some of the compounds revealed better activity.

Pectobacterium carotovorum is a bacterium of the family Enterobacteriaceae; it formerly was a member of the genus Erwinia. The species is a plant pathogen with a diverse host range, including potato, African violet, and other agriculturally and scientifically important plant species. It causes soft rot and blackleg of potato and vegetables, as well as slime flux on many different tree species.[21,22]

Xanthomonas can infect a wide variety of species including pepper, rice, citrus, cotton, tomato, broccoli, cabbage, and soybeans. Some types of Xanthomonas cause localized leaf spot or leaf streak while others spread systemically and cause black rot or leaf blight disease.[23,24]

Pseudomonas syringae is responsible for causing diseases on over 180 plant species including fruit trees, veg-

etable crops and flowers. Pathovars of main economic importance in Europe are the pvs syringae, morsprunorum, avii and persicae, causing bacterial canker on sweet and sour cherry, plum, peach and apricot as well as in wild cherry.[25,26]

Acetylenic esters, alkyl isocyanides, dimethyl acetone-1,3-dicarboxylate and other chemicals were purchased from Fluka and Merck companies. Products were characterized by IR, ^{1}H-NMR and by comparison of their physical properties with those reported in the literature. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ^{1}H-NMR, and ^{13}C-NMR spectra were obtained using a Bruker Avans 400 MHz spectrometer (DRX). Melting points were determined by a Buchi melting point B-540 B. V. CHI apparatus. The elemental analyser was done by Costech ECS 4010 CHNS-O analyser.

EXPERIMENTAL

Preparation of $BF_3.SiO_2$

0.37 g of BF_3 (0.7 ml of $BF_3.Et_2O$) was added drop wise to a mixture of 0.63 g of silicagel and 5 ml of chloroform. The mixture was stirred for 1 h at room temperature. The resulted suspension was filtered. The obtained solid was washed with chloroform and dried at room temperature for 6 h.

General Procedure for the Synthesis of 2-Amino-4*H*-pyran-3,4,5-tricarboxylate Derivative

A mixture of dimethyl acetone-1,3-dicarboxylate (10 mmol, 1.82 ml) and dimethyl or diethyl acetylene dicarboxylate (10 mmol) and $BF_3.SiO_2$ (0.32 g, 25 mol %) in 50 ml H_2O, was added, drop wise at 0 °C over 10 min isocyanide derivatives (10 mmol). The reaction mixture was then allowed to warm up to room temperature and stand for 6 h. After completion of the reaction, the mixture was extracted once with 50 ml toluene, made strongly alkaline with 25% aq. NaOH and then extracted with 2×50 ml toluene. The combined alkaline extracts was dried over $MgSO_4$ and the solvent removed by distillation in a rotovap. All the products were characterized by Melting points, Elemental analyses C, H, and N, IR , ^{1}H-NMR and ^{13}C-NMR. The residual compounds were dissolved in 10 ml EtOAc and 5N HCl/iso-propanol was added in portions until pH 5 was reached. Several times the acid addition had to be stopped and the formed crystals removed by filtration. The salt was then recrystallised in iso-propanol.

Trimetyl 2-(*tert*-butylamino)-6-(2-methoxy-2-oxoethyl)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow oil, yield Solt 3.18 g, 73%, IR (KBr) (υ_{max}/cm^{-1}): 3456, 1744, 1737, 1721, 1683. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.34 (9H, s), 3.64 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 3.85 (2H, s), 4.55 (1H, s), 8.57 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=30.34, 37.68, 37.70, 51.02, 52.17, 52.37, 52.56, 52.38, 72.28, 108.44, 154.48, 160.20, 165.94, 168.56, 169.38, 173.21. Anal calcd for $C_{18}H_{25}NO_9$ (399.4): C, 54.13; H, 6.31; N, 3.51; Found: C, 54.1; H, 6.3; N, 3.5.

Trimetyl 2-(cyclohexylamino)-6-(2-methoxy-2-oxoethyl-4*H*-pyran-3,4,5-tricarboxylate:

White powder mp=116−118 °C, yield Solt 3.23 g 67%, IR (KBr) (υ_{max}/cm^{-1}): 3504, 1744, 1730, 1724, 1686. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.25−2.38 (10H, m), 3.66 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 3.80 (3H, s), 3.94 (2H, s), 4.17 (1H, m), 4.54 (1H, s), 8.39 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=24.42, 25.37, 29.65, 33.30, 33.70, 37.48, 37.87, 48.64, 49.98, 50.93, 52.13, 52.31, 71.68, 108.53, 154.75, 156.91, 159.05, 168.59, 169.21, 173.21. Anal calcd for $C_{20}H_{27}NO_9$ (425.4): C, 56.47; H, 6.40; N, 3.29; Found: C, 56.5; H, 6.4; N, 3.3.

Trimethyl 2-methoxycarbonylmethyl-6-(4-methoxyphenylamino)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow crystal, mp=188−189 °C, yield Solt 3.10 g, 69%, IR (KBr) (υ_{max}/cm^{-1}): 3455, 3012, 1744, 1737, 1728, 1683, 1672, 1612, 1511, 1452, 1253, 1050. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=3.62 (3H, s), 3.67 (s, 3 H), 3.69 (3H, s), 3.70 (3H, s), 3.73 (3H, s), 3.85 (2H, s), 4.55 (1H, s), 7.18 (d, *J*=8.6 Hz, 2H), 7.28 (d, *J*=8.6 Hz, 2H), 8.52 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=30.31, 36.98, 37.30, 50.96, 51.52, 52.31, 52.48, 72.28, 108.44, 120.82, 132.76, 144.25, 145.22, 154.48, 160.20, 165.94, 168.56, 169.38, 173.21. Anal calcd for $C_{21}H_{23}NO_{10}$ (449.4): C, 56.12; H, 5.16; N, 3.12; Found: C, 56.1; H, 5.2; N, 3.1.

3,4-Diethyl 5-methyl 2-(*tert*-butylamino)-6-(2-methoxy-2-oxoethyl)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow oil, yield Solt 3.33 g 72%, IR (KBr) (υ_{max}/cm^{-1}): 3455, 1744, 1738, 1734, 1638. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.24 (3H, t, *J*=8 Hz), 1.31 (3H, t, *J*=8 Hz), 1.38 (9H, s), 3.74 (3H, s), 3.80 (3H, s), 3.98 (2H, s), 4.08−4.25 (4H, m), 4.56 (1H, s), 8.62 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=14.10, 14.75, 30.34, 37.68, 37.89, 52.02, 52.31, 52.44, 59.84, 60.47, 72.47, 108.47, 154.19, 160.06, 166.89, 168.02, 169.57, 172.08. Anal calcd for $C_{20}H_{29}NO_9$ (427.5): C, 56.20; H, 6.84; N, 3.28; Found: C, 56.20; H, 6.8; N, 3.3.

3,4-Diethyl 5-methyl 2-(cyclohexylamino)-6-(2-methoxy-2-oxoethyl)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow oil, yield Solt 3.38 g 69%, IR (KBr) (υ_{max}/cm^{-1}): 3456, 1744, 1740, 1735, 1721. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.24 (3H, t, *J*=8 Hz), 1.30 (3H, t, *J*=8 Hz), 1.53−1.95

(10H, m), 3.74 (3H, s), 3.79 (3H, s), 3.90 (2H, s), 4.03–4.31 (5H, m), 4.55 (1H, s), 8.42 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=14.12, 14.60, 22.37, 24.36, 24.37, 33.28, 33.71, 37.50, 37.93, 49.90, 52.06, 52.30, 59.36, 60.87, 71.73, 108.46, 154.53, 158.85, 166.08, 168.68, 169.00, 172.99. calcd for $C_{22}H_{31}NO_9$ (453.5): C, 58.27; H, 6.89; N, 3.09; Found: C, 58.3; H, 6.9; N, 3.1.

4,5-Diethyl 3-methyl 2-(methoxycarbonylmethyl)-6-(4-methoxy-phenylamino)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow crystal, mp=173–175 ºC, yield Solt 3.44 g, 72%, IR (KBr) (υ_{max}/cm^{-1}): 3455, 3011, 1743, 1736, 1728, 1682, 1672, 1612, 1511, 1452, 1253, 1050. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.22 (3H, t, *J*=8 Hz), 1.30 (3H, t, *J*=8 Hz), 3.64 (3H, s), 3.67 (3 H, s), 3.70 (3H, s), 3.85 (2H, s), 4.10–4.25 (4H, m), 4.55 (1H, s), 7.15 (d, *J*=8.6 Hz, 2 H), 7.27 (d, *J* =8.6 Hz, 2H), 8.57 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=14.21, 14.63, δ=30.34, 37.70, 38.42, 53.18, 51.76, 52.51, 52.38, 71.63, 108.31, 120.69, 132.64, 144.16, 145.01, 154.13, 160.16, 165.88, 168.50, 169.29, 173.08. Anal calcd for $C_{23}H_{27}NO_{10}$ (477.5): C, 57.86; H, 5.70; N, 2.93; Found: C, 58.0; H, 5.7; N, 2.9.

3,4-Di (*tert*-butyl) 5-methyl 2-(*tert*-butylamino)-6-(2-methoxy-2-oxoethyl)-4*H*-pyran-3,4,5-tricarboxylate:

Colourless crystal, mp=103–105 ºC, yield Solt 3.90 g 75%, IR (KBr) (υ_{max}/cm^{-1}): 3456, 1754, 1730, 1728, 1720. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.40 (9H, s), 1.43 (9H, s), 1.53 (9H, s), 3.76 (3H, s), 3.81 (3H, s), 3.89 (2H, s), 4.38 (1H, s), 8.55 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=27.99, 28.54, 30.45, 37.70, 39.45, 51.92, 52.22, 52.32, 73.90, 79.31, 80.45, 108.78, 153.45, 159.71, 166.51, 166.75, 168.76, 172.24. Anal calcd for $C_{24}H_{37}NO_9$ (483.6): C, 59.61; H, 7.71; N, 2.90; Found: C, 59.6; H, 7.7; N, 2.9.

3,4-Di (*tert*-butyl) 5-methyl 2-(cyclohexylamino)-6-(2-methoxy-2-oxoethyl)-4*H*-pyran-3,4,5-tricarboxylate:

Yellow oil, yield Solt 3.82 g 70%, IR (KBr) (υ_{max}/cm^{-1}): 3488, 1747, 1740, 1728, 1686. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.25–1.93 (10H, m), 1.42 (9H, s), 1.50 (9H, s), 3.72(3H, s), 3.77 (3H, s), 3.86 (2H, s), 4.10 (1H, s), 4.35 (1H, s), 8.27 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=27.96, 28.52, 24.62, 24.73, 25.42, 33.46, 33.93, 37.47, 39.46, 50.04, 51.88, 52.26, 73.16, 79.17, 80.45, 108.81, 153.73, 158.54, 166.44, 168.61, 168.80, 172.36. Anal calcd for $C_{26}H_{39}NO_9$ (509.6): C, 61.28; H, 7.71; N, 2.75; Found: C, 61.3; H, 7.7; N, 2.8.

4,5-Di-*tert*-butyl 3-methyl 2-(methoxycarbonyl methyl)-6-(4-methoxy-phenylamino)-4*H*-pyran-3,4,5-tricarboxylyte:

Yellow crystal, mp=162–163 ºC, yield Solt 3.41 g, 64%, IR (KBr) (υ_{max}/cm^{-1}): 3458, 3008, 1743, 1737, 1727, 1683, 1672, 1612, 1511, 1452, 1253, 1050. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.40 (9H, s), 1.43 (9H, s), 3.69 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 3.83 (2H, s), 4.52 (1H, s), 7.10 (d, *J*=8.6 Hz, 2 H), 7.22 (d, *J*=8.6 Hz, 2H), 8.59 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ=28.07, 28.61, 30.42, 37.02, 39.12, 51.17, 52.07, 52.26, 52.38, 73.38, 108.44, 120.82, 132.76, 144.25, 145.22, 154.48, 160.20, 165.94, 168.56, 169.38, 173.21. Anal calcd for $C_{27}H_{35}NO_{10}$ (533.57): C, 60.78; H, 6.61; N, 2.63; Found: C, 60.8; H, 6.6; N, 2.6.

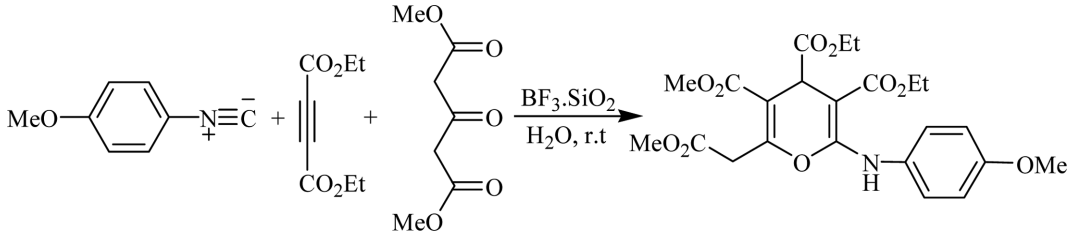
Preparation of Plates and Microbiological Assays

Inoculation of test bacteria (X. campestris pvs, P. syringae and P. carotovorum) was prepared by inoculating a loopful of organism in a 10 ml nutrient broth and incubated at 37 ºC for 24 h each till a moderate turbidity was developed. 0.10 ml of this suspension was thoroughly mixed with 25 ml of nutrient agar medium in each. Presterilized Petri plates and was set aside. After the cooling, the seeded agar plate was used for testing compounds by disc diffusion method. The sterilized paper discs were dipped in each compound solution. These discs were placed in the plates at equidistant. The central disc without any compound was taken as control. The petri plates then incubated at 37 ºC for 24 h. After the recommended period, zones of inhibition were measured. After solidification of medium, 0.10 ml of spore suspension was spread by sterilized spreader in a specific zone. The compounds were dissolved in DMSO solvent in 200 ppm concentration. The paper discs were dipped in each compound solution for 5 min. Then these paper discs were placed equidistant in the plates. The central disc was dipped in DMSO solvent without compound was used as control. These Petri plates were kept for incubation period at 28 ºC for 3 days. After the completion of recommended period, the zones of inhibition were measured (*Table* 3).

RESULTS AND DISCUSSION

In continuation, we have investigated the synthesis of 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivatives in the presence of $BF_3.SiO_2$ via condensation of alkylisocyanides with actylenic esters and dimethyl acetone-1,3-dicarboxylate affords highly functionalized compound (*Scheme* 2).

Herein, we report that $BF_3.SiO_2$ is an efficient catalyst for the synthesis of 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivatives. The reaction of Diethyl 1,3-acetonedicarboxylate (10 mmol, 1.50 ml) with diethyl acetylene dicarboxylate (10 mmol, 1.67 ml) and 4-methoxyphenyl isocyanide (10 mmol, 1.33 g) was investigated for optimization of the reaction conditions (*Scheme* 1 and *Table* 1). The reaction

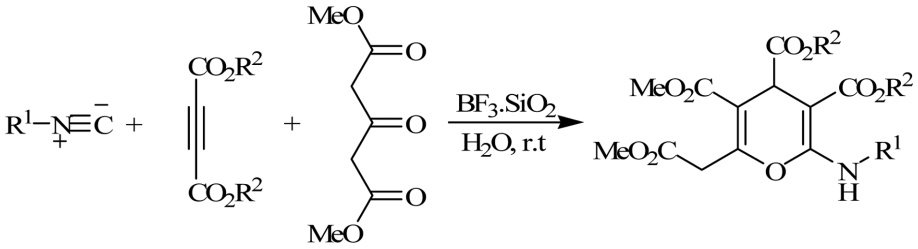


***Scheme* 1.**

***Table* 1.** Synthesis of 4,5-diethyl 3-methyl 2-(methoxycarbonylmethyl)-6-(4-methoxy-phenylamino)-4*H*-pyran-3,4,5-tricarboxylate

Entry	Catalyst (mol %)	Solvent	Conditions	Time (h)	Yield[a] %
1	$BF_3.SiO_2$ (25)	Chloroform	r.t.	6	61
2	$BF_3.SiO_2$ (25)	Ethanol	r.t.	6	38
3	$BF_3.SiO_2$ (25)	Water	r.t.	3	46
3	$BF_3.SiO_2$ (25)	Water	50°C	6	scarce
3	$BF_3.SiO_2$ (25)	Water	r.t.	6	64
4	$BF_3.SiO_2$ (25)	Solvent-free	r.t.	6	50

[a]Isolated yield



***Scheme* 2.**

***Table* 2.** Synthesis of 2-amino-3-cyano-1,4,5,6-tetrahydropyrano[3,2-c]quinolin-5-one derivatives[a] via *Scheme* 2

Entry	R^{1b}	R^2	Time (h)	Yield[c] %	Mp (°C) [Rep]
1	t-But	Me	6	73	Oil [Oil][20]
2	c-Hexyl	Me	6	67	116–118 [116–118][20]
3	4-Methoxyphenyl	Me	6	69	188–189
4	t-But	Et	6	72	Oil[Oil][20]
5	c-Hexyl	Et	6	69	Oil
6	4-Methoxyphenyl	Et	6	72	173–175
7	t-But	t-But	6	75	103–105 [103–105][20]
8	c-Hexyl	t-But	6	70	Oil [Oil][20]
9	4-Methoxyphenyl	t-But	6	69	162–163

[a]The dimethyl acetone-1,3-dicarboxylate (10 mmol, 1.82 ml) and acetylene dicarboxylate (10 mmol) in the presence of (0.32 g) of freshly prepared 37% $BF_3.SiO_2$ in H_2O at room temperature.
[b]All the products were characterized by IR and ^{1}H-NMR.
[c]Isolated yield.

revealed that the best conditions were in H_2O at room temperature.

Dimethyl acetone-1,3-dicarboxylate with dimethyl or diethyl acetylene dicarboxylate and various isocyanide were used as substrates for the synthesis of 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivatives derivatives in H_2O at room temperature (*Scheme* 2 and *Table* 2).

We have synthesized a novel class 2-amino-4*H*-pyran derivative as potential antibacterial agents. In vitro antibacterial assay was performed against X. campestris pvs, P. syringae and P. carotovorum by using the disc diffusion method.[27,28] The results obtained as zone of inhibition (mm) are presented in *Table* 3. Tetracycline was used as standard drugs for the assay. The concentration used for the test com-

***Table* 3.** Analytical and antibacterial activity of compounds

Entry	R^1	R^2	Molecular Formula	Molecular weight	Zone of inhibition in (mm)		
					X. campestris pvs	P. syringae	P. carotovorum
1	t-But	Me	$C_{18}H_{25}NO_9$.HCl	435.85	22 ± 0.9	24 ± 0.7	22 ± 0.8
2	c-Hexyl	Me	$C_{20}H_{27}NO_9$.HCl	481.69	19 ± 1.1	23 ± 1.2	26 ± 1.0
3	4-Methoxyphenyl	Me	$C_{21}H_{23}NO_{10}$.HCl	485.11	19 ± 1.1	23 ± 1.2	25 ± 0.9
4	t-But	Et	$C_{20}H_{29}NO_9$.HCl	461.91	28 ± 0.4	32 ± 1.0	32 ± 0.7
5	c-Hexyl	Et	$C_{22}H_{31}NO_9$.HCl	489.94	23 ± 0.8	28 ± 0.4	28 ± 1.1
6	4-Methoxyphenyl	Et	$C_{23}H_{27}NO_{10}$.HCl	513.92	17 ± 1.2	20 ± 0.8	21 ± 1.2
7	t-But	t-But	$C_{24}H_{37}NO_9$.HCl	520.01	14 ± 0.5	24 ± 1.5	21 ± 0.5
8	c-Hexyl	t-But	$C_{26}H_{39}NO_9$.HCl	546.05	25 ± 1.3	28 ± 1.1	26 ± 1.2
9	4-Methoxyphenyl	t-But	$C_{27}H_{35}NO_{10}$.HCl	570.03	21 ± 1.3	23 ± 1.1	24 ± 1.0
Tetracyclin					24 ± 0.7	27 ± 1.1	25 ± 0.8

pounds and that of the standard drugs remains the same. It is observed from Table 1 that 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivative have exhibited moderate activity. When 2-amino-4*H*-pyran-3,4,5-tricarboxylate derivatives were salt compound, there are high enhancement in the activity and solubility in water. Further, these functionalities were substituted with various groups like 3,4,5-tricarboxylate and 2-methoxy-2-oxoethyl since in the earlier studies it has been shown that the presence of one or more of the aforesaid would lead to the improvement of the activity.

CONCLUSION

In conclusion, the reactions of alkyl isocyanides with electron deficient acetylenic esters in the presence of dimethyl acetone-1,3-dicarboxylate provides a simple one-pot entry in to the synthesis of poly functional 4*H*-pyran derivatives of potential synthetic interest. All synthesized compounds have shown good activity against the pathogenic bacteria.

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