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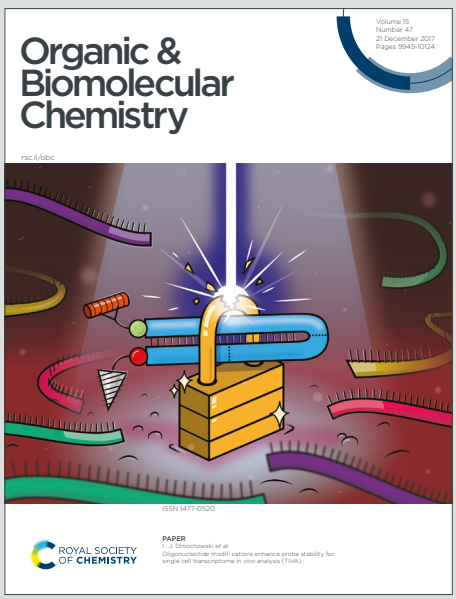

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ARTICLE

Ni(II)-catalyzed vinylic C-H functionalization of 2-acetamido-3-arylacrylates to access isotetronic acids

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A ligand-free Ni(II)-catalyzed cascade annulation reaction for the synthesis of 4-aryl-substituted isotetronic acids from 2-acetamido-3-arylacrylates via vinylic C-H functionalization is reported. The reaction proceeds through heteroatom guided electrophilic insertion of nickel to the vinylic double bond followed by annulation with dibromomethane. This unconventional route features cascade steps, sole product formation, multiple functional group tolerance, low cost of catalysts and reagents, and readily available starting materials. Using this method, various aryl-substituted isotetronic acids have been synthesized which are biologically relevant. The annulation of 2-acetamido-3-arylacrylates has also been assessed with 1,2-dichloroethane, which resulted in the rearranged annulated products of 5-methyl substituted isotetronic acids.

Introduction

Isotetronic acids are an important scaffold of natural products[1] exhibiting important activities (Fig. 1), such as antitumor, aldose reductase inhibitory[2] activities, etc. For example, butyrolactone I (**1a**)[3a] is a potent and selective inhibitor of CDK1 and CDK2, important for regulating the cell cycle.[3b] Aspernolide A (**1b**) exhibits antiproliferative activity against colon and pancreatic carcinoma.[3c] WF-3681 (**2**), a fungal metabolite, is an aldose reductase inhibitor.[2] Sotolon (**3**) is useful as a powerful odorant.[4a] Compound **4** is a potent anti-oxidant and anti-inflammatory agent.[4b] Xenofuranones A (**5a**) and B (**5b**) might be involved directly in the nematode symbiosis.[4c] Serpenone (**6**) and its synthetic analogs are used for the treatment of diabetic neuropathy.[4d] Structure **7** represents a group of nonsteroidal anti-inflammatory drugs (NSAID), which are selective COX-2 inhibitors.[4e,f] Compound **8** is a fungicide.[4g] Compound **9** shows potent 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) inhibitory activity. It also acts as a bleaching herbicide for the control of grass and broadleaf weeds.[5] Thus the wide range of bioactivities of these compounds (Fig. 1) has drawn attention of scientists from various fields. Many approaches were reported for the synthesis of isotetronic acids and their derivatives. Usually, base mediated homoaldol reaction of α-keto esters are utilized for the synthesis of racemic mixture of isotetronic acids[3b] or their *O*-protected derivatives[6]. High yielding regioselective[7a] and enantioselective[7b] routes to isotetronic acids are also reported from α-keto esters. Interestingly, Tius *et al.* have reported an unusual oxidative cyclization pathway using selenium dioxide on α,β-unsaturated methyl ketones to access isotetronic acids.[8]

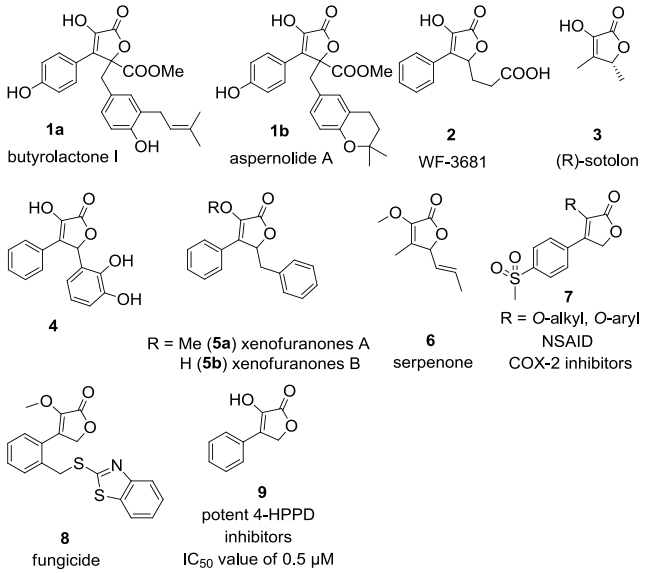

Fig. 1 Examples of some naturally occurring and bioactive isotetronic acids (**1-9**).

The major limitations of these routes are (i) inaccessibility of starting α-keto esters, very few of which are commercially available and synthesis of substituted α-keto esters are not easy.[8] (ii) in a side reaction, homoaldolisation[3b,6] of α keto ester occurs.

Herein, we now report a ligand free Ni(II) catalyzed cascade reaction for the synthesis of 3-hydroxy-4-arylfuran-2(5*H*)-ones (**9a-9t**) from 2-acetamido-3-arylacrylates (**10**) via vinylic C-H functionalization (Scheme 1). Acetamidoacrylates were previously used for the synthesis of oxazoles *via* vinylic C-H functionalization by hypervalent iodine mediated intramolecular oxidative cyclization (Scheme 1) by Zhao and coworkers.[9] Koenig *et al.* reported a $Pd(OAc)_2$ catalyzed *ortho* C-H activation of 2-acetamido-3-arylacrylates for the synthesis of

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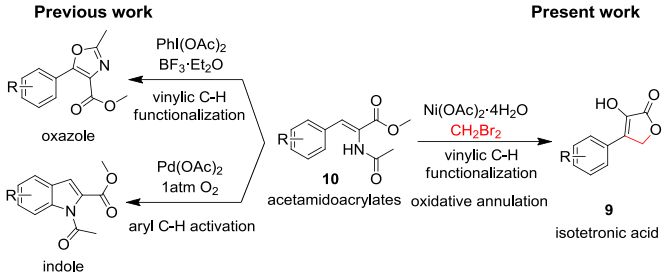


Scheme 1 Intramolecular C–H functionalization reactions with 2-acetamido-3-arylacrylates.

indole-2-carboxylate derivatives (Scheme 1) and used oxygen as the terminal oxidant.[10]

Hence, the reactivities of aryl amidoacrylates have drawn considerable attention and inspired us to study its reactivity towards vinylic C-H and ortho aryl C-H positions by employing dibromomethane both as the solvent and alkylating agent and palladium acetate as catalyst. We have found that no trace amount of ortho-substituted product was formed, instead, substitution at the vinylic position is achieved resulting in the formation of cyclized isotetronic acid as the sole product with the formation of one C-C bond and one C-O bond.

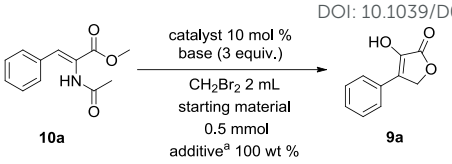
Our newly developed methodology reports a [4+1] annulation[11a] reaction leads to the formation of a heterocyclic core,[11b,c] it has some advantages like (i) all reagents are of low cost and the starting materials can be easily synthesized by one-pot reaction from aromatic aldehydes.[12] (ii) vinylic functionalization of acetamidoacrylate directly leads to the sole product i.e. iotetronic acid via cascade of steps. (iii) multiple functional groups are tolerated.

Results and discussion

The use of dibromomethane as bridging methylene group has been discussed previously by Yu *et al.*[13] for phthalide synthesis from benzoic acids. Following the similar reaction conditions as reported by Yu *et al.*,[13] we examined the reaction of 2-acetamido-3-phenylacrylate (**10a**) with three equivalents of K_2HPO_4 as base, dibromomethane as solvent and 10 mol% $Pd(OAc)_2$ as catalyst at 120 °C in nitrogen atmosphere (Table 1, entry 1). No trace amount of *ortho*-substituted product was formed. Instead, we noted the formation of *C*-4-aryl-substituted isotetronic acid **9a** with 10% yield and 60% recovery of starting material after 72 h. The product **9a** was characterized by ^1H, ^{13}C NMR [14] and HRMS spectroscopic techniques. The structure of **9a** was further confirmed by using Single-crystal X-ray diffraction (Table 2).

An attempt has also been made to optimize the reaction conditions (Table 1 & Table S1). The reaction yield was negligibly affected by the change of bases (Table S1, entries 1-4). A slight improvement of the yield was observed when acetates of alkali metals were used (Table 1, entries 2-6). Increased loading of the palladium catalyst from 10 to 15 mol % resulted in the decrease of reaction yield by 1 % (Table 1, entry 3). Increasing the amount of KOAc from 3 to 5 equivalents did not result in any change in

Table 1 optimization of reaction



Entry	Base	Catalyst	Temp °C	Time (h)	Yield[b] 9 (%)
1[c,d]	K_2HPO_4	$Pd(OAc)_2$	120	72	10
2	KOAc	$Pd(OAc)_2$	135	48	22
3	KOAc	$Pd(OAc)_2$ / 15 mol%	135	48	21
4	NaOAc	$Pd(OAc)_2$	135	48	20
5	CsOAc	$Pd(OAc)_2$	140	48	17
6	KOAc (5equiv.)	$Pd(OAc)_2$	140	48	21
7	-	$Pd(OAc)_2$	135	48	0
8	KOAc	-	135	48	0
9[e]	KOAc	$Pd(OAc)_2$	135	48	26
10	$Li(OAc).2H_2O$	$Pd(OAc)_2$	140	48	41
11	$Li(OAc).2H_2O$	$Pd(OAc)_2$	140	48	49
12[f]	$Li(OAc).2H_2O$	$Pd(OAc)_2$	140	48	0
13	$Li(OAc).2H_2O$	$Ni(PCy_3)_2Cl_2$	140	48	62
14	$Li(OAc).2H_2O$	$Ni(PCy_3)_2Cl_2$	150	48	69
15	$Li(OAc).2H_2O$	$Ni(PCy_3)_2Cl_2$	150	36	58
16[g]	$Li(OAc).2H_2O$	$Ni(OAc)_2.4H_2O$ (2 mol %)	150	15	**81**
17[g]	$Li(OAc).2H_2O$	$Ni(Cl)_2.6H_2O$ (2 mol %)	150	22	72
18[g]	$Li(OAc).2H_2O$	$Ni(NO_3)_2.4H_2O$ (2 mol %)	150	22	70

a = 100 wt % molecular sieve was used entries 11 to 18 except 15, b = Yield was determined after column chromatographic purification; all the compounds were added under: c = nitrogen atmosphere, d = air; In all the cases 2 mL dibromomethane was used as solvent, except e = (1 mL / 1 mL) CH_2Br_2 / DMF, f = DCM (2 mL), g = (2 mL / 0.5 mL) CH_2Br_2 / DMF was added as solvent.

yield (Table 1, entry 6). No reaction occurred when the reaction was carried out without base (Table 1, entry 7) and catalyst (Table 1, entry 8). The reaction was carried out with different solvent systems (Table S1, entries 12-14) but only a slight improvement in yield was observed when DMF (normal) and CH_2Br_2 were used (Table 1, entry 9). A significant improvement of the yield was achieved in the presence of three equivalents of $LiOAc{\cdot}2H_2O$ as base (Table 1, entry 10). This may be explained by the fact that Li^+ interacts strongly with amide compared to other alkali metals, such as Na^+ and K^+.[15] Addition of 100 wt % 4 Å molecular sieve dust with respect to acetamidoacrylates increased the yield to 49% (Table 1, entry 11).[16] The reaction does not proceed with dichloromethane (Table 1, entry 12).

Finally, we shifted to nickel(II) catalyst (Table 1, entry 13), which resulted in significant improvement of yields. Both palladium and nickel salts gave the same product, but nickel was found to be more efficient catalyst in this reaction. Temperature optimization was carried out with bis(tricyclohexylphosphine)nickel(II) dichloride as catalyst (Table S1, entries 19-21), and the best result was obtained at

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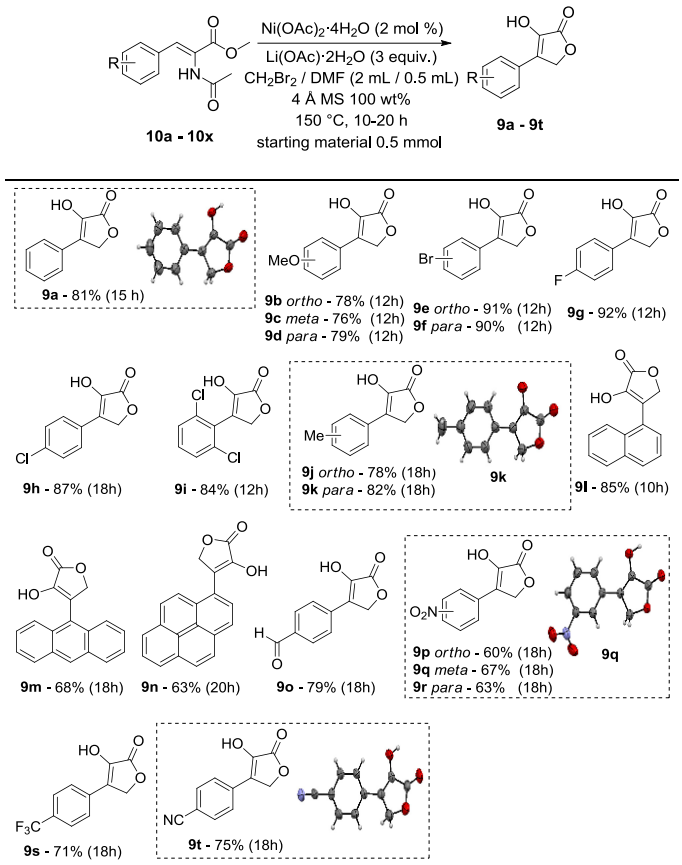
Table 2 Substrate scope

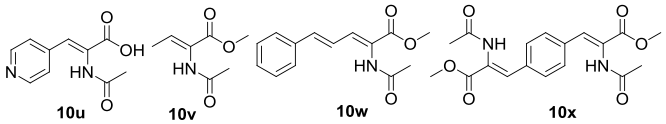


150 °C. A yield of 69% was achieved along with 8% starting material recovery (Table 1, entry 14). A significant drop in yield was observed in the absence of molecular sieves (Table 1, entry 15). A number of nickel(II) catalyst of varying mol% were screened (Table 1, entries 16-18 & Table S1, entries 24-30). Best results were obtained by employing 2 mol% $Ni(OAc)_2{\cdot}4H_2O$ as catalyst with 0.5 mL DMF along with 2 mL dibromomethane as a mixed solvent, resulting in sole product formation with 81% yield and complete consumption of starting material after 15 h (Table 1, entry 16).

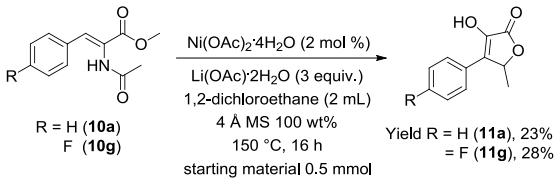
Under the above optimized conditions, we have successfully synthesized twenty analogs of **9a** (Table 2). All the compounds were thoroughly characterized by ^1H, ^{13}C NMR and HRMS techniques (sampling cone 10 eV). We obtained the single-crystal structures for some of the synthesized isotetronic acids (Table 2). Our methodology is found to be consistent with the substrates containing both electron-donating and withdrawing groups in aryl ring with good to excellent yield. Halogen-containing compounds (**10e-10i**) were not only tolerated but also obtained in good yields. A formyl group in **10o** was well tolerated under the reaction conditions.

However, hetero aryl-substituted substrate (**10u**) was found to decompose (**Table 3**). The pyridine derivative (**10u**) might form complex with nickel[17] and get decomposed at high temperature. No positive outcome was obtained with **10v** to **10x** due to decomposition and/or polymerization.

Table 3 Acetamidoacrylates with different outcome of the cascade reaction

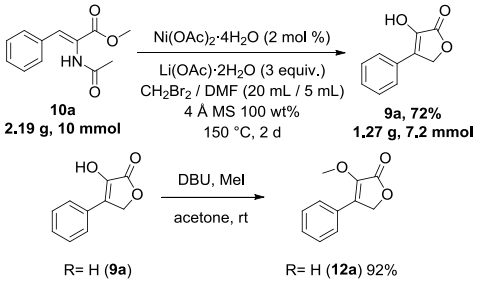


The positive outcome of nickel(II)-catalyzed isotetetronic acids synthesis from acetamidoacrylates and dibromomethane encouraged us to further investigate whether six-membered cyclic product 3-hydroxy-4-phenyl-5,6-dihydro-2H-pyran-2-one derivatives with 1,2-dibromoethane[13] can be obtained. Unfortunately, the reaction did not take place with 1,2-dibromoethane. Interestingly, the similar reaction with 1,2-dichloroethane successfully gave rearranged product, i.e., 5-methyl-substituted isotetronic acids **11a** and **11g** with moderate yields. Various reaction conditions (similar to Table 1) were screened with nickel(II)-catalysts, but no improvement of the yield was observed (Scheme 2).



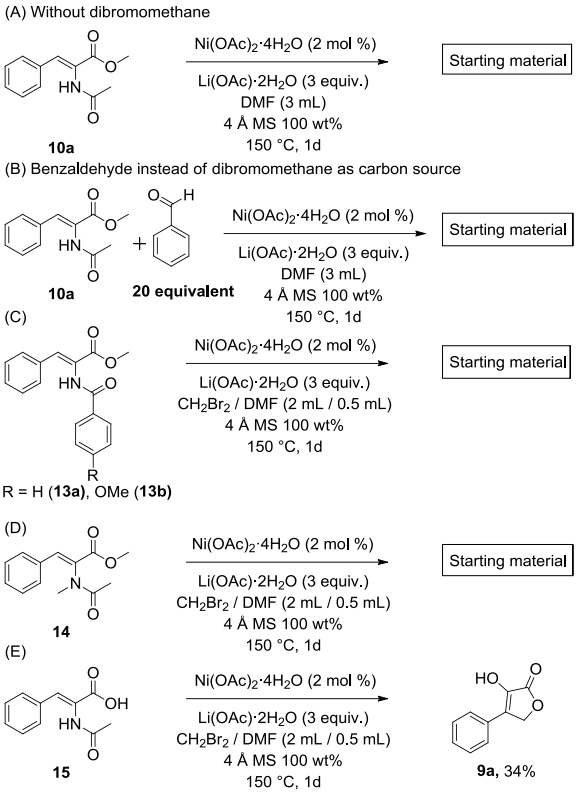
Scheme 2 Synthesis of 5-methyl-substituted isotetronic acid *via* Ni(II)-catalyzed cascade reaction of acetamidoacrylates.

Our methodology merits greater significance due to its applicability in the gram-scale synthesis of isotetronic acids with reduced (half) solvent amount. A 10 mmol scale reaction was undertaken with compound **10a** which resulted in 72% isolated yield of **9a** after 48 h (Scheme 3). Compound **9a** was also methylated to obtain *O*- protected isotetronic acid **12a**, using DBU and methyl iodide in acetone[18] (Scheme 3).



Scheme 3 Gram scale synthesis of **9a** and synthesis of o-methy ether (**12a**) of synthesized isotetronic acid.

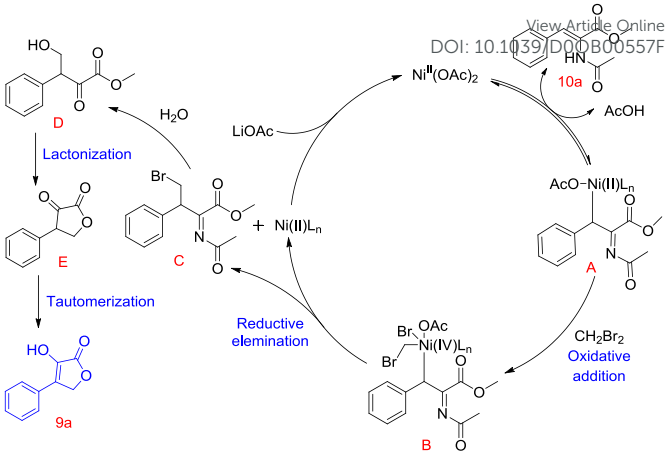
Some different sets of reactions have also been carried out to understand the mechanism of the reaction. At first, to understand the carbon source at C-5 of isotetronic acid, we carried out the reaction without dibromomethane (Scheme 4A). As expected, no reaction took place and starting material remained intact. We tried the reaction with excess benzaldehyde instead of dibromomethane along with DMF as



Scheme 4 Supporting reactions.

solvent, keeping other conditions same (Scheme 4B). This has been done to check whether our starting material acetamidoacrylate in the reaction condition hydrolyzed to form β-keto ester and follow a normal aldol reaction with benzaldehyde. But no product was formed and starting material remained intact. Formation of compound **9o** (Table 2) also supports this assumption, where an existing formyl group was present in the aromatic ring. From the result, we can assume that hydrolysis of the amide group might occur after the new C-C bond formation with dibromomethane (Scheme 5). When we used benzoyl protection instead of acetyl (**13a** and **13b** in Scheme 4C) and N-methyl acetamidoacrylate **14** (Scheme 4D), no reaction took place and starting material remained intact. This may be explained by the fact that benzoyl protected and N-methyl acetylacrylate unable to form complex with nickel (Scheme 5). From the result, we conclude that both the electron density and the presence of N-H bond is required for the heteroatom directed metallation step. Next, we also think about the possibility of ester hydrolysis at the beginning of the reaction. To check this possibility, we have taken 2-acetamido-3-phenylacrylic acid (Scheme 4E) instead of its methyl ester, which results in poor yield. This might be due to its decomposition at higher temperature via decarboxylation.

Based on these results and literature reports,[13,19,20] a plausible mechanistic pathway for the formation of isotetronic acid is presented in Scheme 5. Initially, heteroatom-guided[19a,b] electrophilic nickelation takes place with acetamidoacrylate derivative **10a** to form intermediate **A**, which then undergoes



Scheme 5 A plausible mechanistic pathway for **9a**.

oxidative addition with dibromomethane[13] forming possible nickel(IV)-intermediate **B**.[20] Reductive elimination from Ni(IV)-intermediate **B** furnishes bromo derivative **C**. which undergoes hydrolysis to afford alcohol **D**. Lactonization followed by tautomerization gives isotetronic acid **9a**.

Conclusions

In summary, we have, for the first time, reported C-H functionalization to access isotetronic acids. The reaction proceeds via vinylic C-H functionalization of 2-acetamido-3-arylacrylate derivatives with inexpensive nickel catalyst and dibromomethane. The proposed methodology is compatible with both electron-donating as well as electron-withdrawing groups. The positive aspects of the reaction are sole product formation, no requirement of external oxidants and applicability in the gram-scale. We have successfully synthesized twenty analogs of **9a** and two C-5 methyl-substituted isotetronic acids. Our future goals are to establish the reaction conditions for the synthesis of C-5 methyl-substituted isotetronic acids and apply them in the synthesis of bioactive molecules.

Experimental

General experimental details

Addition of all the reagents and solvents were performed under air for GP-I and GP-II. Glassware used in the reactions was thoroughly oven-dried. All commercial grade reagents were used without further purification and solvents were dried prior to use following standard protocol. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 pre-coated plates (0.25 mm) and the spots were visualized by exposure to UV light and/or by dipping into $KMnO_4$ solution. Silica gel of particle size 230–400 mesh and petroleum ether/ethyl acetate as eluent were used for column chromatographic purification. ^1H and ^{13}C NMR spectra for all the compounds were recorded at 400/600 and 100/150 MHz (BrukerUltrashield™ 400, Ascend™ 600), respectively. The spectra were recorded in deuterochloroform ($CDCl_3$) and

deuterated dimethyl sulfoxide (DMSO-d_6) as solvent at room temperature. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$: δ_H = 7.26, δ_C = 77.16 ppm and DMSO-d_6: δ_H = 2.5, δ_C = 39.52 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet q: quartet, dt: doublet of triplets, br: broad.), coupling constant (Hz), integration. Data for ^{13}C NMR are reported as chemical shift. HRMS spectra using ESI (+ ve) 70 eV for amidoacrylates and 10eV for isotetronic acid were recorded on an ESI-FTMS mass spectrometer.

General procedure (GP-1) for the synthesis of acetamidoacrylates (10a-10x):

Acetamidoacrylate derivatives were synthesized from corresponding aromatic aldehydes and *N*-acetylglycine using literature known procedure.[12]

To a suspension of *N*-acetylglycine (1 equiv) in dry benzene (5mL/mmol) containing Et_3N (1.5 equiv), ethyl chloroformate (1.1 equiv) was added at 0 °C and the mixture was stirred at room temperature until the *N*-acetylglycine crystals disappeared and triethylamine hydrochloride separated. The aldehyde (0.5 equiv) was added to the mixture and heated under reflux at 80 °C for 2h. After cooling to room temperature, triethylamine hydrochloride was removed by suction filtration and washed twice with dry benzene. The combined solution was concentrated and dried under reduced pressure. The residue was then dissolved in methanol (HPLC grade, 5mL/mmol), Et_3N (1.5 equiv) was added and refluxed at 65 °C for 3h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. Purification of the residue by silica gel flash column chromatography using EtOAc/Hexanes as eluent or trituration afforded the desired acetamidoacrylates (**10a-10x**).

Experimental details and characterization data for acetamidoacrylates (10a-10x): Yields and characterization data are given below for each product. Most of the synthesized acetamidoacrylates are literature known (see S.I. pages, S4 – S7). Characterization data for the unknown acetamidoacrylates are given below.

(Z)-methyl 2-acetamido-3-(2,6-dichlorophenyl)acrylate (10i):

The titled compound **10i** was synthesized from 2,6-dichlorobenzaldehyde (500 mg, 2.857 mmol) according to **GP-1**. Purification was done by flash column chromatography using 25% ethyl acetate in hexane as eluent to afford white solid product (567 mg, 1.97 mmol, yield = 69%); m.p. = 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.23 (m, 3H), 7.19–7.15 (m, 2H), 3.88 (s, 3H), 1.97 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.8, 165, 147.2, 133.3, 131.3, 129.6, 129.1, 127.6, 125.6, 124.8, 53.1, 23.4; FT-IR ῡ 3310, 3085, 2954, 1717, 1694, 1652, 1496, 1425, 1365, 1284, 1136, 782 cm^{-1}; HRMS (ESI-TOF) calculated for $C_{10}H_{12}Cl_2NO_3$ $[M+H]^+$ 288.0194; found 288.0192.

(Z)-methyl 2-acetamido-3-(naphthalen-1-yl)acrylate (10l):

The titled compound **10l** was synthesized from 1-naphthaldehyde (1 g, 6.41 mmol) according to **GP-1**. The crude product was dissolved in acetone and triturated with hexane. The mixture was filtered and dried *in vacuo*. The pure product was obtained as a white solid (1.293 g, 4.79 mmol, yield = 75%); m.p. = 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.69 (m, 4H), 7.61–7.39 (m, 4H), 6.91 (s, 1H), 3.90 (s, 3H), 1.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.9, 165.5, 133.7, 131.3, 129.6, 128.84, 128.5, 127.7, 126.9, 126.4, 125.4, 124.4, 52.9, 23.2; FT-IR ῡ 3229, 3046, 3007, 2953, 1720, 1656, 1637, 1517, 1429, 1249, 1124, 968, 770 cm^{-1}; HRMS (ESI-TOF) calculated for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1130, found 270.1126.

(Z)-methyl 2-acetamido-3-(anthracen-9-yl)acrylate (10m):

The titled compound **10m** was synthesized from anthracene-9-carbaldehyde (300 mg, 1.456 mmol) according to **GP-1**. The crude product was dissolved in acetone and triturated with hexane. The mixture was filtered and dried *in vacuo*. The pure product was obtained as a yellow solid (288 mg, 0.903 mmol, yield = 62%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.08–7.92 (m, 4H), 7.82 (s, 1H), 7.57–7.42 (m, 4H), 6.56 (s, 1H), 3.96 (s, 3H), 1.65 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.7, 165, 131.3, 130.9, 129.1, 129.1, 128.4, 126.7, 126.6, 125.6, 125.3, 52.9, 22.8; FT-IR ῡ 3292, 3050, 2960, 1705, 1678, 1635, 1494, 1436, 1370, 1251, 1007, 745, 629 cm^{-1};HRMS (ESI-TOF) calculated for $C_{20}H_{18}NO_3$ $[M+H]^+$ 320.1284; found 320.1281.

(Z)-methyl 2-acetamido-3-(pyren-1-yl)acrylate (10n):

The titled compound **10n** was synthesized from pyrene-1-carbaldehyde (500 mg, 2.174 mmol) according to **GP-1**. The crude product was dissolved in acetone and triturated with hexane. The mixture was filtered and dried *in vacuo*. The pure product was obtained as a yellow solid (478 mg, 1.39 mmol, yield = 64%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.40–8.06 (m, 9H), 7.93 (s, 1H), 3.82 (s, 3H), 1.89 (d, *J* = 11.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 169.5, 165.5, 131.1, 130.7, 130.3, 129.1, 128.6, 128, 127.4, 127.2, 126.6, 126.5, 125.8, 125.7, 124.8, 123.9, 123.7, 123.6, 52.3, 22.3; FT-IR ῡ 3229, 3038, 3003, 2952, 1730, 1657, 1517, 1429, 1240, 1124, 838, 714 cm^{-1}; HRMS (ESI-TOF): calculated for $C_{22}H_{18}NO_3$ $[M+H]^+$ 344.1285; found 344.1281.

(Z)-methyl 2-acetamido-3-(4-formylphenyl)acrylate (10o):

The titled compound **10o** was synthesized from terephthalaldehyde (2.2 g, 16.418 mmol) according to **GP-1**. Purification was done by flash column chromatography using 25% ethyl acetate in hexane as eluent to afford white solid product (2.93 g, 11.82 mmol, yield = 72%); m.p. = 148-150 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 9.83 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.17 (s, 1H), 3.72 (s, 3H), 2.01 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.5, 169.4, 165.3, 139.3, 135.8, 130.1, 129.5, 128.8, 128.5, 52.3, 22.4; FT-IR ῡ 3227, 2999, 2951, 2851, 2742, 1723, 1697, 1661, 1643, 1513, 1246, 1211, 1131, 1013, 744 cm^{-1}; HRMS (ESI): calculated for $C_{13}H_{14}NO_4$ $[M+H]^+$ 248.0920; found 248.0917.

(Z)-methyl 2-acetamido-3-(2-nitrophenyl)acrylate (10p):

The titled compound **10p** was synthesized from 2-nitrobenzaldehyde (500 mg, 3.31 mmol) according to **GP-1**. Purification was done by flash column chromatography using

30% ethyl acetate in hexane as eluent to afford white solid product (526 mg, 1.986 mmol, yield = 60%); m.p. = 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.73 (s, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.12 (s, 1H), 3.90 (s, 3H), 1.97 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 167.8, 165, 147.2, 133.3, 131.3, 129.6, 129.1, 127.6, 125.6, 124.8, 53.1, 23.4; FT-IR ῡ 3024, 3149, 3077, 3001, 2949, 1726, 1652, 1638, 1518, 1357, 1249, 1130, 985 cm^{-1}; HRMS (ESI): calculated for $C_{12}H_{13}N_2O_5$ $[M+H]^+$ 265.0820; found 265.0819.

(Z)-methyl 2-acetamido-3-(4-(trifluoromethyl)phenyl)acrylate (10s):

The titled compound **10s** was synthesized from 4-(trifluoromethyl)benzaldehyde (500 mg, 2.873 mmol) according to **GP-1**. The crude product was dissolved in acetone and triturated with hexane. The mixture was filtered and dried *in vacuo*. The pure product was obtained as a white solid (660 mg, 2.3 mmol, yield = 80%); m.p. = 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.43 (m, 5H), 7.26 (s, 1H), 3.77 (s, 3H), 1.99 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.7, 165.4, 137.5, 131.1, 130.8, 130.5, 130.1, 129.7, 129.6, 127.9, 125.7, 125.3, 125.2, 122.5, 119.8, 77.4, 77.1, 76.8, 52.9, 23.3; FT-IR ῡ 3216, 2957, 2853, 1730, 1664, 1649, 1523, 1321, 1244, 1164, 1124, 1066, 1015, 836, 745 cm^{-1}; HRMS (ESI): calculated for $C_{13}H_{13}F_3NO_3$ $[M+H]^+$ 288.0841; found 288.0842.

(2Z,2'Z)-dimethyl 3,3'-(1,4-phenylene)bis(2-acetamidoacrylate) (10x):

The titled compound **10x** was synthesized from compound **10o** (700 mg, 2.822 mmol) according to **GP-1**. The crude product was dissolved in acetone and triturated with hexane. The mixture was filtered and dried *in vacuo*. The pure product was obtained as a white solid (437 mg, 1.213 mmol, yield = 43%). m.p. = 160-162 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.71 (s, 1H), 7.68 (s, 2H), 7.17 (s, 1H), 3.72 (s, 3H), 2.02 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.5, 165.6, 137.7, 129.7, 125.5, 122.6, 53.1, 23.6; FT-IR ῡ 3233, 2920, 2851, 2750, 1713, 1664, 1640, 1428, 1362, 1245, 1126, 966, 733 cm^{-1}; HRMS (ESI): calculated for $C_{18}H_{21}N_2O_6$ $[M+H]^+$ 361.1396; found 361.1394.

General procedure (GP-2) for the synthesis of isotetronic acids (9a-9t):

In a 15 ml pressure tube, acetamidoacrylate **10** (0.5 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (2 mol%), $Li(OAc){\cdot}2H_2O$ (3 equiv.), 4 Å Molecular Sieve dust (100 wt% with respect to acetamidoacrylate), were taken. Then CH_2Br_2 (2 mL) and DMF (0.5 mL) were added in open atmosphere and heated at 150 °C (**Caution**: Keep the reaction inside the hood and bring it to room temperature for monitoring the reaction). After completion of reaction (10-20 h, checked by TLC), add EtOAc into the reaction mixture and filtered through a short pad of cellite, solvent was evaporated under reduced pressure. Purification was done by silica gel flash column chromatography using EtOAc/Hexanes as eluent to afford the desired isotetronic acid.

Experimental details and characterization data:

3-hydroxy-4-phenylfuran-2(5H)-one (9a):

The titled compound **9a** was synthesized from compound **10a,** according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (71 mg, 81%). m.p. = above 200 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 7.71-7.69 (m, 2H), 7.46-7.44 (m, 2H), 7.37-7.36 (m, 1H), 5.18 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, DMSO) δ 170.1, 137.5, 130.8, 128.8, 126.3, 126, 67.6; FT-IR ῡ 3298, 3053, 2939, 1719, 1683, 1451, 1399, 1322, 1163, 1027, 757, 685 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_9O_3$ $[M+H]^+$ 177.0552; found 177.0546.

Gram scale synthesis of 3-hydroxy-4-phenylfuran-2(5H)-one (9a): In a 100 ml pressure tube, acetamidoacrylate **10a** (2.190 g, 10 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (50 mg, 2 mol%) $Li(OAc){\cdot}2H_2O$ (3.06 g, 3 equiv.), 4 Å Molecular Sieve (2.2 g, 100 wt%), were taken. Then CH_2Br_2 (20 mL) and DMF (5 mL) were added and heated at 150 °C. After completion of reaction (48 h, checked by TLC), add EtOAc into the reaction mixture and filtered through a short pad of cellite, solvent was evaporated under reduced pressure. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (1.27 g, 72%).

3-hydroxy-4-(2-methoxyphenyl)furan-2(5H)-one (9b):

The titled compound **9b** was synthesized from compound **10b,** according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (80 mg, 78%). m.p. = 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 1H), 7.41 – 7.37 (m, 1H), 7.12 – 7.08 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 156.3, 136.8, 130.8, 129.1, 124.4, 121.9, 119.6, 111.9, 69.4, 56.1; FT-IR ῡ 3265, 2922, 2851, 1727, 1493, 1463, 1394, 1314, 1251, 1163, 1020, 763 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_4$ $[M+H]^+$ 207.0657; found 207.0652.

3-hydroxy-4-(3-methoxyphenyl)furan-2(5H)-one (9c):

The titled compound **9c** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (78 mg, 76%); m.p. = above 200 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.58 (s, 1H), 5.13 (s, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171, 159.9, 136.5, 131.1, 130, 126, 118.8, 115.25, 112.3, 68.3, 55.4; FT-IR ῡ 3266, 2919, 2852, 1719, 1678, 1461, 1394, 1322, 1163, 1034, 770 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_4$ $[M+H]^+$ 207.0657; found 207.0654.

3-hydroxy-4-(4-methoxyphenyl)furan-2(5H)-one (9d):

The titled compound **9d** was synthesized from compound **10d,** according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (81 mg, 79%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 5.09 (s, 2H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 171.4, 160.6, 134.9, 128.4, 126.7, 122.8, 114.6, 68.3, 55.5; FT-IR ῡ 3266, 2923, 2852, 1717, 1688, 1603, 1457, 1689, 1310, 1216, 1163, 1127, 825, 771 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_4$ $[M+H]^+$ 207.0657; found 207.0657.

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4-(2-bromophenyl)-3-hydroxyfuran-2(5H)-one (9e):

The titled compound **9e** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (116 mg, 91%); m.p. = 145-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 6.8 Hz, 1H), 5.24 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 138.1, 134, 131.4, 131.1, 130.8, 127.8, 127.4, 121.8, 69.8; FT-IR ῡ 3251, 2923, 2853, 1741, 1472, 1396, 1307, 1264, 1162, 1029, 767, 654 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8BrO_3$ $[M+H]^+$ 254.9657; found 254.9662.

4-(4-bromophenyl)-3-hydroxyfuran-2(5H)-one (9f):

The titled compound **9f** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (115 mg, 90%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.72 – 7.56 (m, 4H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 169.8, 138.1, 131.7, 129.9, 128.2, 124.7, 121.8, 67.4; FT-IR ῡ 304, 2971, 1726, 1451, 1388, 1230, 1166, 1025, 993, 827, 771, 678 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8BrO_3$ $[M+H]^+$ 254.9657; found 254.9679.

4-(4-fluorophenyl)-3-hydroxyfuran-2(5H)-one (9g):

The titled compound **9g** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (89 mg, 92%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.75 (s, 2H), 7.30 (t, *J* = 8.2 Hz, 2H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 169.9, 163.1, 160.6, 137.1, 128.5, 128.5, 127.3, 125.1, 115.8, 115.6, 67.4; FT-IR ῡ 3310, 2922, 2852, 1739, 1514, 1458, 1398, 1231, 1166, 1830, 841, 771 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8FO_3$ $[M+H]^+$ 195.0457; found 195.0439.

4-(4-chlorophenyl)-3-hydroxyfuran-2(5H)-one (9h):

The titled compound **9h** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (92 mg, 87%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.33 (s, 1H), 5.10 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 137.9, 133.1, 129.6, 128.8, 128, 124.7, 67.4; FT-IR ῡ 3280, 2919, 2851, 1718, 1679, 1494, 1450, 1387, 1162, 1032, 770, 722, 651 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8ClO_3$ $[M+H]^+$ 211.0162; found 211.0157.

4-(2,6-dichlorophenyl)-3-hydroxyfuran-2(5H)-one (9i):

The titled compound 9i was synthesized according to GP-2. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (103 mg, 84%); m.p. = 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.29 (m, 1H), 6.69 (s, 1H), 5.02 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 139.1, 135.2, 131.1, 128.4, 128, 124.3, 68.6; FT-IR ῡ 3252, 3084, 1750, 1737, 1557, 1429, 1391, 1317, 1158, 1025, 893, 775, 725 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_7Cl_2O_3$ $[M+Na]^+$ 244.9772; found 244.9767.

3-hydroxy-4-(o-tolyl)furan-2(5H)-one (9j):

The titled compound **9j** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (74 mg, 78%); m.p. = 157-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 4H), 6.57 (s, 1H), 5.13 (s, 2H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 137.2, 136.8, 131.2, 129.5, 129.2, 128.7, 128.2, 126.1, 70, 20.7; FT-IR ῡ 3256, 3065, 3025, 1719, 1491, 1449, 1390, 1304, 1168, 1031, 893, 759, 721 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708; found 191.0703.

3-hydroxy-4-(p-tolyl)furan-2(5H)-one (9k):

The titled compound **9k** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (78 mg, 82%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 10.57 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.14 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 170.1, 138.4, 136.8, 129.3, 127.9, 126.3, 126.2, 67.5, 21; FT-IR ῡ 3293, 2920, 2852, 1723, 1452, 1312, 1231, 1155, 1024, 768 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708; found 191.0713.

3-hydroxy-4-(naphthalen-2-yl)furan-2(5H)-one (9l):

The titled compound **9l** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (96 mg, 85%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 -7.89 (m, 3H), 7.59 – 7.43 (m, 4H), 6.15 (s, 1H), 5.14 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 137.5, 134, 130.4, 130.3, 128.9, 127.5, 127.1, 126.7, 126.3, 125.6, 125.3, 70.3; FT-IR ῡ 3195, 2923, 2854, 1726, 1436, 1351, 1253, 1150, 1116, 1020, 772, 627 cm^{-1}; HRMS (ESI): calculated for $C_{14}H_{11}O_3$ $[M+H]^+$ 227.0708; found 227.0693.

4-(anthracen-9-yl)-3-hydroxyfuran-2(5H)-one (9m):

The titled compound **9m** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 25% ethyl acetate in hexane as eluent to afford white solid product (93 mg, 68%); m.p. = 171-173 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.50 (m, 4H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 139.6, 131.5, 129.7, 129.2, 129.1, 127.1, 125.8, 124.9, 70.7; FT-IR ῡ 3290, 3056, 2926, 2854, 1753, 1444, 1335, 1286, 1156, 1123, 1030, 737 cm^{-1}; HRMS (ESI): calculated for $C_{18}H_{13}O_3$ $[M+H]^+$ 277.0865; found 277.0859.

3-hydroxy-4-(pyren-1-yl)furan-2(5H)-one (9n):

The titled compound **9n** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 25% ethyl acetate in hexane as eluent to afford white solid product (94 mg, 63%); m.p. = above 200 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.45 (s, 1H), 8.371- 8.352 (m, 3H), 8.29 – 8.21 (m, 3H), 8.17 – 8.09 (m, 3H), 5.36 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, DMSO) δ 170.2, 138.8, 131.6, 131.2, 130.9, 128.5, 128.4, 128.4, 128.1, 127.7, 127, 126.6, 126.4, 126.1, 126.1, 126, 125.2, 124.5, 124.2, 69.8; FT-IR ῡ 3334, 3258, 3040, 2921, 2851, 1755, 1391, 1329, 1297, 1150, 845, 720 cm^{-1}; HRMS (ESI): calculated for $C_{20}H_{13}O_3$ $[M+H]^+$ 301.0865; found 301.0878.

4-(4-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)benzaldehyde (9o):

The titled compound **9o** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 20% ethyl acetate in hexane as eluent to afford white solid

product (81 mg, 79%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 10.01 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 5.23 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 192.6, 169.7, 139.8, 136.4, 135.4, 129.8, 126.7, 124.1, 67.6; FT-IR ῡ 3288, 2923, 2853, 1731, 1697, 1606, 1393, 1320, 1219, 1170, 1027, 830, 772 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_9O_4$ $[M+H]^+$ 205.0501; found 205.0482.

3-hydroxy-4-(2-nitrophenyl)furan-2(5H)-one (9p):

The titled compound **9p** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 20% ethyl acetate in hexane as eluent to afford white solid product (66 mg, 60%); m.p. = 140-142 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.75 (s, 1H), 8.04 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.79 (td, *J* = 7.7, 1.1 Hz, 1H), 7.71 – 7.60 (m, 2H), 5.14 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, DMSO) δ 168.7, 148.5, 139, 133.4, 130.1, 129.9, 124.9, 124.7, 124, 68; FT-IR ῡ 2923, 2853, 1763, 1528, 1352, 1156, 1028, 749 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8NO_5$ $[M+H]^+$ 222.0402; found 222.0399.

3-hydroxy-4-(3-nitrophenyl)furan-2(5H)-one (9q):

The titled compound 9q was synthesized according to GP-2. Purification was done by flash column chromatography using 20% ethyl acetate in hexane as eluent to afford white solid product (74 mg, 67%); m.p. = above 200 °C; ^{1}H NMR (600 MHz, DMSO) δ 11.40 (s, 1H), 8.58 (s, 1H), 8.20 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 5.26 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, DMSO) δ 169.5, 148.1, 139.4, 132.3, 132, 130.3, 123.3, 122.9, 120.7, 67.5 (s); FT-IR ῡ 3267, 2933, 2854, 1730, 1529, 1352, 1156, 957, 751 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8NO_5$ $[M+H]^+$ 222.0402; found 222.0409.

3-hydroxy-4-(4-nitrophenyl)furan-2(5H)-one (9r):

The titled compound **9r** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 20% ethyl acetate in hexane as eluent to afford white solid product (70 mg, 63%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.30 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 5.24 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 169.5, 146.4, 140.6, 137.2, 127.1, 124, 122.9, 67.5; FT-IR ῡ 3273, 2924, 2854, 1760, 1525, 1351, 1170, 751 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_8NO_5$ $[M+H]^+$ 222.0402; found 222.0412.

3-hydroxy-4-(4-(trifluoromethyl)phenyl)furan-2(5H)-one (9s):

The titled compound **9s** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (87 mg, 71%); m.p. = above 200 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.26 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 5.20 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 169.7, 139.4, 134.7, 128.8, 128.5, 128.2, 127.9, 126.8, 125.6, 125.6, 125.6, 125.5, 125.5, 123.8, 122.8, 120.1, 67.5; FT-IR ῡ 3284, 2964, 1742, 1396, 1327, 1153, 1102, 1060, 1016, 844, 771, 641 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_8F_3O_3$ $[M+H]^+$ 245.0426; found 245.0419.

4-(4-hydroxy-5-oxo-2,5-dihydrofuran-3-yl)benzonitrile (9t):

The titled compound **9t** was synthesized according to **GP-2**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (75 mg, 75%); m.p. = above 200 °C; ^{1}H NMR (600 MHz, DMSO) δ 11.43 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 5.20 (s, 2H). ^{13}C{^{1}H} NMR (150 MHz, DMSO) δ 169.5, 140, 135.2, 132.6, 126.7, 123.4, 118.7, 110.4, 67.4; FT-IR ῡ 3273, 2923, 2853, 2229, 1727, 1462, 1397, 1317, 1171, 1029, 841, 771 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_8NO_3$ $[M+H]^+$ 202.0504; found 202.0509.

General procedure (GP-3) for synthesis of 5-methyl-substituted isotetronic acid:

In a 15 ml pressure tube, acetamidoacrylate **10** (0.5 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (2 mol %) $Li(OAc){\cdot}2H_2O$ (3 equiv.), 4 Å Molecular Sieve (100 wt% with respect to acetamidoacrylate), were taken. Then DCE (2 mL) was added in open atmosphere and heated at 150 °C (**Caution**: Keep the reaction inside the hood and bring it to room temperature for monitoring the reaction). After completion of reaction (12-15 h, checked by TLC). Add EtOAc into the reaction mixture and filtered through a short pad of cellite, solvent was evaporated under reduced pressure. Purification of the residue by silica gel chromatography using EtOAc/Hexanes as eluent afforded the desired isotetronic acid. Yields and characterization data are given below for each product.

Experimental details and characterization data:

Methyl (*Z*)-2-acetamido-3-phenylacrylate (11a):

The titled compound **11a** was synthesized according to **GP-3**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (22 mg, 23%); m.p. = 104-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.62 (m, 2H), 7.47 – 7.40 (m, 2H), 7.40 - 7.36 (m, 1H), 6.40 (s, 1H), 5.47 (q, *J* = 6.5 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 136.4, 131.4, 129.9, 129.3, 129, 127.7, 76.5, 20.4; FT-IR ῡ 3289, 3061, 2924, 2854, 1724, 1450, 1393, 107, 1157, 1057, 881, 764, 694 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708; found 191.0702.

4-(4-fluorophenyl)-3-hydroxy-5-methylfuran-2(5H)-one (11g).

The titled compound **11g** was synthesized according to **GP-3**. Purification was done by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford white solid product (29 mg, 28%); m.p. = 117-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.56 (m, 4H), 7.15 (t, *J* = 8.6 Hz, 4H), 6.66 (s, 2H), 5.43 (q, *J* = 6.4 Hz, 2H), 1.57 (d, *J* = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 164.2, 161.7, 136.3, 130.6, 129.7, 129.6, 126.3, 126.2, 116.4, 116.1, 76.3, 20.4; FT-IR ῡ 3302, 2922, 2867, 1740, 1566, 1459, 1401, 1166, 1026, 771 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{10}FO_3$ $[M+H]^+$ 209.0614; found 209.0618.

General procedure (GP-4) for synthesis of o-methyl ether of isotetronic acid:

DBU (1.3 equiv.) was added to a stirred solution of isotetronic acid derivative (1 equiv.) in acetone (5 mL) and the reaction was stirred for 15 min. at 0 °C. Iodomethane (2 equiv.) was added dropwise. Ice bath was removed after 10 min. and stirring was continued for 4 h at room temperature. After completion of reaction the solvent was removed, and the residue was diluted with EtOAc. The resulting solution was washed successively with HCl (5 mL, 1 N), water (3 x 20 ml), saturated aqueous solution of $Na_2S_2O_3$ (2 mL), and brine. The combined organic

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layers were dried using Na_2SO_4, concentrated *in vacuo*, and purified on silica gel column using EtOAc/Hexanes eluent.

Experimental details and characterization data:

Methyl (*Z*)-2-acetamido-3-phenylacrylate (12a):

The titled compound **12a** was synthesized from 0.2 mmol **9a** according to **GP-4**. Purification was done by flash column chromatography using 5% ethyl acetate in hexane as eluent to afford white solid product (35 mg, 92%); m.p. = 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.65 (m, 2H), 7.45 – 7.38 (m, 3H), 5.08 (s, 2H), 4.15 (s, 3H). $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$) δ 169.1, 140.1, 134, 130, 130, 129, 126.8, 67.4, 58.6; FT-IR ῡ 2924, 2852, 1732, 1650, 1457, 1354, 1148, 1076, 1021, 978, 758, 683 cm^{-1}; HRMS (ESI): calculated for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708; found 191.0708.

Conflicts of interest

There are no conflicts to declare.

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