Multistep microwave assisted solvent free green chemical synthesis of 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione

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A novel class of biologically active compound 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione (**10a–b**)has been achieved efficiently and quickly under solvent free conditions in an open vessel microwave system. The multi step one pot synthesis involved the reaction of 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione (**6a–d**) and glyoxylic acid monohydrate followed by cyclocondensation with hydrazine hydrate under microwave irradiation. The synthesis of 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione(**6a–d**) has also been described from the reaction of (2-oxo-1,2-dihydroquinolin-4-yl)hydrazine with 1,3-cyclohexanedione in the absence of any solvent/catalyst/strong acid or solid support using microwaves.

Keywords: 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione

Pyridazinoquinoline is an important nucleus, which has been extensively used in medicinal chemistry, including many patented clinical examples.[1-5] They have also known to possess antiparkinsonism[6] and neuroprotectant activity for treatment of stroke,[7] as platelet aggregation inhibitors[8] and also useful as important intermediate in the area of organic synthesis.[9] Scanty reports mention the conventional synthesis of pyridazinoquinolindione involving the multistep reaction of 2-carbomethoxyester of quinoline with acid,[10] benzo-γ-carboline with *O*-mesityl sulfonyl hydroxalamine (MSH),[11] isatin with 2-oxosuccinate diester,[12] aryl hydrazine with acid chloride,[13] acid chloride with pyrrolidine and BOC-protected hydrazines.[10]

Indolo[3,2-*c*]quinolines are present in many naturally occurring alkaloids[14] and used as anticancer,[15] antitumoral,[16] antineoplastic,[17] glycine site NMDA receptor,[18] cytotoxic agent[19] and antibacterial agents.[20] The synthesis of indolo [3,2-*c*]quinolines has been studied extensively involving the multistep reaction of *O*-azidobenzaldehyde and triphenyl-phosphonium bromide,[21] intermolecular Heck cyclisation of 2-iodophenyl-3-indolecarboximide with triphenylphosphine,[22] Aza-witting reaction of iminophosphorane with aromatic isocynates,[23] coupling and cyclisation reaction of 2-phenyl quinoline derivatives,[24] reaction of 2-chloroquinoline and benzotriazole followed by cyclisation,[25] Buchward-Hartwing amination and Pd catalyst reaction of 2-chloroaniline with 4-chloro quinoline,[26] cyclisation reaction of hydrazone,[27,28] multistep indolisation of 1,2,3,4-tertahydro-4-oxo-quinolone phenylhydrazone,[29] alkylation of oxindoles with *p*-nitro-benzylchloride,[30] condensation of phenylhydarzine with 2,3-dihydroquinolinone,[31] *etc*.

All these methods suffers many disadvantages like multistep tedious procedure involving prolonged refluxing using environmentally unacceptable reagents, volatile solvents and using strong acids (PPA, H_2SO_4, *etc*.) with tedious work up procedure involving further use of solvents.

In spite of immense biological activities of pyridazino-quinoline and indolo[3,2-*c*]quinolines less attention has been paid on the pentacyclic heterocyclic ring system involving indole, quinoline and pyridazine nucleus in a single molecular frame work. Recently a new class of DNA intercalcators based on the 10*H*-indolo[3,2-*c*]pyridazino[1,6-*a*]quinolinium ion was synthesised by the Westphal reaction[32] of carbolinium derivatives with various 1,2-dicarbonyl compounds.

Recent years have witnessed the importance of microwaves in mediating organic reactions[33-35] because of their advantages with respect to classical organic chemistry in terms of shorter reaction times, minimum waste, generally higher yields, possibility of carrying out reactions in the absence of solvents and in safe conditions.

In continuation of our earlier interest on molecular diversity and search for new leads in drug designing programme in the synthesis of molecules,[36] which are novel yet resemble known biological active molecules by virtue of the presence of some critical structural features, we report our results on the use of microwave technique in a multistep synthesis of a novel 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione (**10**) which combines these three biolabile components together to give compact structure such as the title compound.

Synthetic strategies (Scheme 1) of this novel nucleus involves the reaction of biologically active alkaloid key intermediate 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione (**6a–d**) with glyoxylic acid monohydrate under solvent free condition in open vessel microwave system using few drops of DMF which act as homogeniser and energy transfer agent[37] to give 2-hydroxy-2-(6,7-dioxo-6,7,8,9,10, 11-hexahydro-5*H*-indolo[3,2-*c*]quinolin-8-yl)acetic acid (**9**) in reasonable purity (TLC) which on subsequent neat reaction with hydrazine hydrate in absence of any solvent/catalyst/ support gave 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione (**10a–b**) efficiently and quickly in reasonable purity with no need for further purification in

Table 1 Spectral and physical data of synthesised compounds **9,10 a–b**

Cmpd	R_1	R_2	Time/min.	Yield*/%	M.p./°C	Molecular formula	Elemental analyses (observed/calculated)		
			Δ/ MW	Δ/ MW			C	H	N
9a	OCH_3	H	900/4	62/85	154	$C_{18}H_{16}N_2O_6$	60.84/60.67	4.51/4.53	7.81/7.86
9b	Cl	H	840/5	60/86	212	$C_{17}H_{13}N_2ClO_5$	56.78/56.60	3.65/3.63	7.74/7.77
10a	OCH_3	H	3000/2	40/88	228	$C_{18}N_{13}N_4O_3$	64.48/64.66	4.20/4.22	16.71/16.76
10b	Cl	H	3060/3	45/85	260	$C_{17}H_{10}N_4ClO_2$	60.08/60.28	3.26/3.27	16.49/16.54

*Isolated yield.

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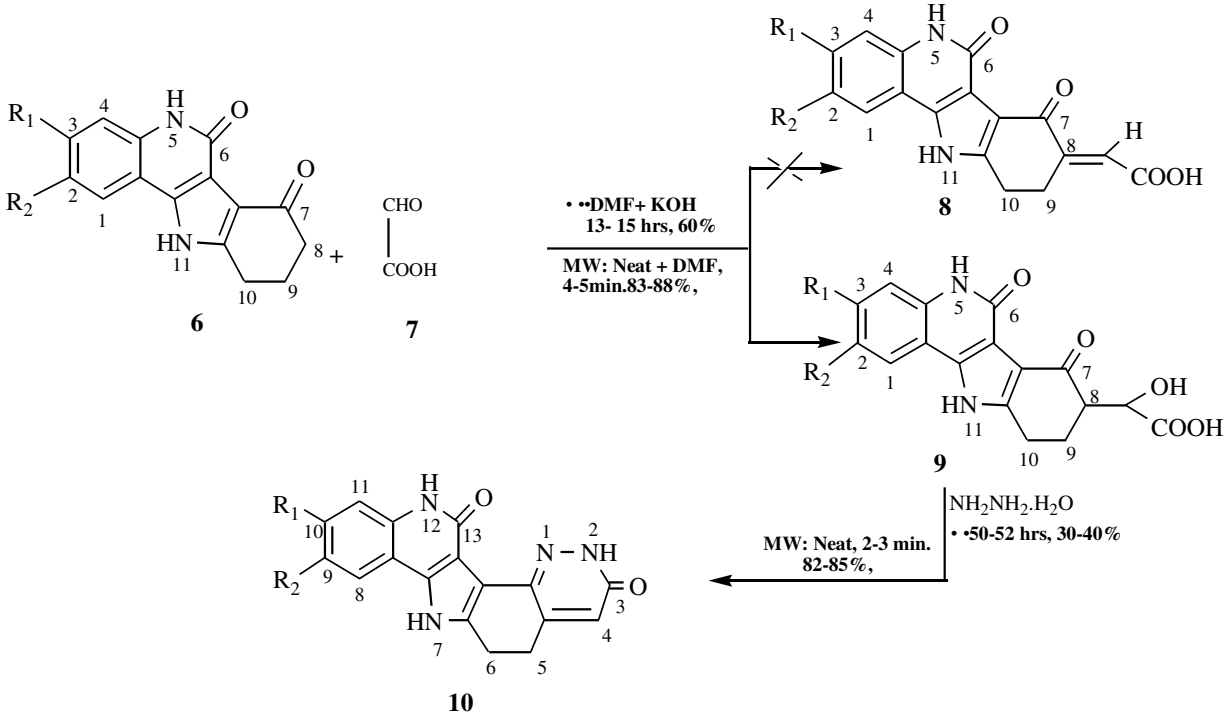


Scheme 1

85–88% yield in 3–5 min in one pot. Conventionally the title compounds are synthesised in lower yield after refluxing 50–60 h.

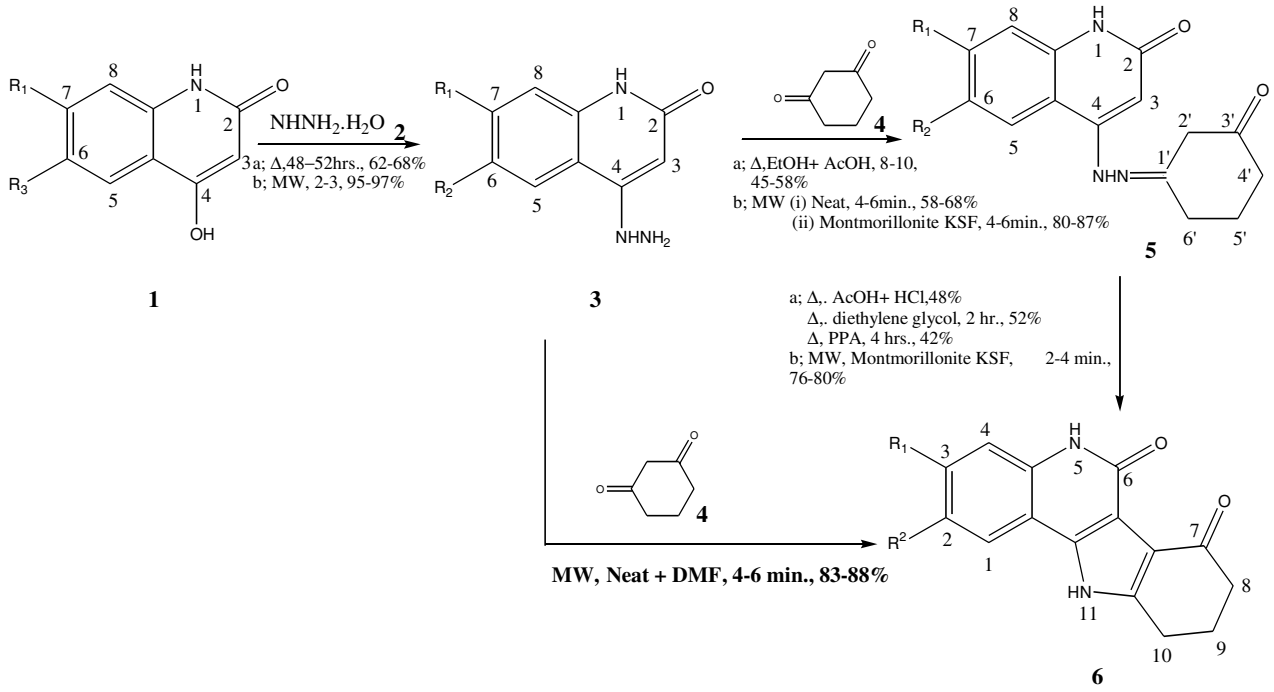
We have also improved the synthesis of the key intermediate 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinolin-6,7(5*H*)-dione which act as a promising chemotherapeutic agent and found in many naturally occurring alkaloids by Fischer indole cyclisation of (2-oxo-1,2-dihydroquinolin-4-yl)hydrazine (**3**) and 1,3-cyclohexanedione (**4**) under microwaves in absence of any solvent, catalyst or solid support. (2-Oxo-1,2-dihydroquinolin-4-yl)hydrazine (**3**) was also synthesised by improved microwave induced procedure by neat reaction of 4-hydroxyquinolin-2-(1H)-one with hydrazine hydrate in quantitative yield.[38] Recently in our laboratory substituted 4-hydroxyquinolin-2(1*H*)-one was also synthesised by improved microwave enhanced environmentally acceptable procedure by reacting substituted anilines with malonic acid in neat conditions using a few drops of DMF,[39] thus making the whole procedure as facile, rapid and environmentally benign (Scheme 2).

Although some Fischer indole cyclisation have already been performed under MW irradiation, Abrnovitch and Bulman[40] reported the cyclisation using 96% formic acid, while Srider[41] carried out condensation in acetic acid under microwaves. Later Loupy *et al.*[42] reported the synthesis of 2-pyridyl-indole by Fischer indole cyclisation using clayzic under focused microwaves. To the best of our knowledge we report here for the first time the synthesis of 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione using microwaves in a green chemical approaches. Non reproducibility of results observed by some workers in domestic microwave oven, can be over come by previous cartography of energy distribution[43] and performing the reactions under continuous microwave power emission without on-off cycles. The reactions carried out with similar weight of load always located in the same place as determined above in the oven are highly reproducible in present studies.

In classical thermal heating reaction occurred in two steps. At first cyclohexane-1,3-dione (2-oxo-1,2-dihydroquinoline-4-yl)hydrazone(**5**) is formed, which was subjected to Fischer indole cyclisation in presence of acetic acid and conc. HCl/PPA in dry conditions[16] to give 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione (**6**) in lower yield. Under microwaves encouraging results were obtained when same reaction was carried out under different reaction conditions. In neat conditions no cyclisation occurred, only cyclohexane-1,3-dione (2-oxo-1,2-dihydroquinolin-4-yl)hydrazone is formed in lower yield. While with few drops of DMF, Fischer indole cyclisation occurred efficiently and quickly in one step without formation of hydrazone derivatives in significant yields with higher purity (Table 2). Small quantity of DMF was sufficient to increase the reaction temperature and consequently enhanced the reaction. This ability of DMF to act as energy transfer and dehydrating agents was yet recently advocated.[37]

When same reaction was carried out using solid acid Montmorillonite KSF, at first step cyclohexane-1,3-dione (2-oxo-1,2-dihydroquinolin-4-yl)hydrazone (**5**) is formed which on further irradiation under the same reaction conditions gave 8,9,10,11 tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione (**6**) in comparatively lower yield (Table 2).

4-Hydroxyquinolin-2-(1H)-one (**1**) treated with hydrazine hydrate afforded the (2-oxo-1,2-dihydroquinoline-4-yl) hydrazine (**3**), instead of corresponding hydrazone. IR spectrum of **3** showed absorption bands at 3380–3270 cm^{-1} (NH stretching) and 1640–1650 cm^{-1} (NH–C=O). In ^1H NMR spectrum of **3a** showed a broad signal at δ 6.92 ppm for two protons of NH_2 and singlet at δ 8.72 and δ 9.18 for both NH proton. All these are D_2O exchangeable. These compounds were found to be insoluble in NaOH solution. Presence of C=O at 1640–1650 and disappearance of broad band at 3450 cm^{-1} (OH) in IR spectra and peak at δ 11.2 ppm for OH proton in ^1H NMR spectra, further confirmed the formation of **3** instead of 4-hydroxyquinoline-2(1*H*)-one hydrazone. In ^{13}C NMR spectrum of **3a** showed characteristic peak of C-$NHNH_2$ at δ161.8 and 164.2 for C=O, further confirmed the formation of title product. (Table 3).



Scheme 2

Table 2 Physical data of synthesised compounds **3, 5** and **6**

Cmpd	R_1	R_2	Time/min	Yield/%	M.p./°C	Molecular formula	Elemental analysis (observed/calculated)		
							C	H	N
3a	OCH_3	H	3	96	268	$C_{10}H_{11}N_3O_2$	58.70/58.53	5.38/5.40	20.41/20.48
3b	H	CH_3	2.5	95	255	$C_{10}H_{11}N_3O$	63.28/63.48	5.84/5.86	22.14/22.21
3c	Cl	H	3.5	97	245	$C_9H_8N_3ClO$	51.40/51.56	3.83/3.85	19.97/20.04
3d	H	OCH_3	3	95	202	$C_{10}H_{11}N_3O_2$	58.68/58.53	5.41/5.40	20.41/20.48
5a	OCH_3	H	4[a]/5[b]	68[a]/82[b]	205	$C_{16}H_{17}N_3O_3$	64.38/64.20	5.70/5.72	13.99/14.04
5b	H	CH_3	6[a]/4[b]	65[a]/80[b]	178	$C_{16}H_{17}N_3O_2$	67.62/67.83	6.03/6.05	14.78/14.83
5c	Cl	H	4[a]/6[b]	62[a]/85[b]	192	$C_{15}H_{14}N_3ClO_2$	59.14/59.31	4.63/4.65	13.78/13.83
5d	H	OCH_3	4[a]/5[b]	58[a]/87[b]	152	$C_{16}H_{17}N_3O_3$	63.99/64.20	5.73/5.72	14.08/14.04
6a	OCH_3	H	2[c]/4[b]	80[c]/85[d]	270	$C_{16}H_{14}N_2O_3$	67.86/68.07	4.98/5.00	9.89/9.92
6b	H	CH_3	3[c]/4[d]	78[c]/83[d]	230	$C_{16}H_{14}N_2O_2$	72.37/72.16	5.28/5.30	10.48/10.52
6c	Cl	H	4[c]/6[d]	80[c]/88[d]	215	$C_{15}H_{11}N_2ClO_2$	62.64/62.84	3.82/3.84	9.74/9.77
6d	H	OCH_3	2[c]/4[d]	76[c]/84[d]	265	$C_{16}H_{14}N_2O_3$	67.26/68.07	5.01/5.00	9.95/9.92

[a]Yield and time in case of reaction in neat conditions; [b]yield and time in case of reaction using montmorilonite KSF; [c]yield and time in case of two step reaction using mont. KSF; [d]yield and time in case of one step reaction using few drops of DMF.

The (2-oxo-1,2-dihydroquinoline-4-yl)hydrazine (**3**) react with 1,3-cyclohexanedione under microwaves in neat condition gave hydrazone derivatives (**5**). IR spectrum of **5a** showed disappearance of NH_2 band at 3380–3270 cm^{-1} and appearance of an additional band of C=O at 1720 of cyclohexanone along with usual band of amide at 1640 and C=N at 1620 cm^{-1}. ^1H NMR spectrum of **5a** showed absence of signal at δ 6.92 which was present in compound **3a** for two protons of NH_2 group and presence of signals as multiplets at δ1.46–1.52 (m, 2H, CH_2, C_5'), δ 1.78–1.84 (m, 2H, CH_2, C_6'), δ 2.11–2.14 (m, 2H, CH_2, C_4') and singlet at δ 2.78 ppm (s, 2H, CH_2) for C_2' methylene protons and at 6.85 for CH proton of quinolinone ring respectively. ^{13}C NMR spectrum of **5a** showed peaks at 188.4 (C=O), 168.3 (C=O), 161.5 (C-$NHNH_2$), 160.2 (C-OCH_3), 109.5–136.4(aromatic carbons), 98.4 (CH, C_3), 56.8 (OCH_3), 39.6 (CH_2, C_2'), 32.7

Table 3 Spectral data of synthesised compounds **3,5,6 a–e, 9a–b, 10a–b**

Cmpd	IR(cm^{-1})	^1H NMR(δ,ppm)				^{13}C NMR	
		CH_2	CH_3/OCH_3/CH	Ar–H	NH/NH_2/OH	(δ,ppm) *m/z*(%)	Mass
3a	3340–3020 (br NH, NH_2 & CH str), 1650 (s, C=O), 1605 (s), 1140–1120 (C–O–C)	–	3.86 (s, 3H, OCH_3), 6.38 (s, 1H, CH)	6.93 (d, *J*=2 Hz, H–8), 7.30(dd, *J*=2+7 Hz H–6), 7.91(d, *J*=7 Hz H–5)	6.92 (br, 2H, NH_2), 8.72 (s, 1H, NH), 9.18(s, 1H)	56.7 (OCH_3), 92.4 (CH), 110.2–136.9 (aromatic carbons), 160.2 (C–OCH_3), 161.8 (C–$NHNH_2$), 164.2 (C=O)	–

Table 3 *continued*

Cmpd	IR(cm^{-1})	^{1}H NMR(δ,ppm)				^{13}C NMR	
		CH_2	CH_3/OCH_3/CH	Ar–H	NH/NH_2/OH	(δ,ppm) *m/z*(%)	Mass
3b	3330–3010 (br, NH, NH_2 & CH str), 1665 (s, C=O), 1610 (s)	–	2.73 (s, 1H, CH_3), 6.25 (s, 1H, CH)	6.90 (d, *J*=2 Hz, H–8), 7.39 (dd, *J*=2+7 Hz H–7), 8.02 (d, *J*=7 Hz H–5)	6.95 (br, 2H, NH_2), 8.25 (s, 1H, NH), 9.02(s, 1H, NH)	22.4 ($\underline{C}H_3$), 90.2 ($\underline{C}H$), 109.5–135.4 (aromatic carbons), 161.4 (C–$NHNH_2$), 165.4 (C=O)	–
3c	3320–2990 (br, NH,NH_2, CH str.), 1640 (s, C=O), 1605 (s), 780 (C–Cl)	–	6.42 (s, 1H, CH)	7.01(d, *J*=8 Hz, H–8), 7.42(dd, *J*= 2+ 7 Hz H–6), 8.12 (d, *J*= 2 Hz, H–5)	6.98 (br, 2H, NH_2), 8.15(s, 1H, NH), 9.05(s, 1H, NH)	–	–
3d	3360–3020 (br, NH, NH_2& CH str.), 1650 (s, C=O), 1602(s), 1140–1120 (C–O–C)	–	3.78 (s, 3H, OCH_3), 6.85 (s, 1H, CH)	6.95 (d, *J*=2 Hz, H–8), 7.52(dd, *J*=2+7 Hz H–7), 8.23 (d, *J*=7 Hz H–5)	6.92 (br, 2H, NH_2), 8.26 (s, 1H, NH), 9.31(s, 1H, NH)	–	–
5a	3210 (br, NH), 3080–3020 (br, CH str.), 1720 (s, C=O),1640 (s, NH–C=O) 1605 (s), 11400–1120 (C–O–C)	1.46 (m, 2H, C_5'), 1.78(m, 2H, C_6'), 2.11 (m, 2H, C_4'), 2.78 (s, 2H, C_2')	3.84 (s, 3H, OCH_3), 6.85 (s, 1H, CH)	6.90 (d, *J*=2 Hz, H–8), 7.25 (dd, *J*=2+7 Hz H–6), 7.98 (d, *J*=7 Hz H–5)	8.55 (s, 1H, NH), 10.24 (s, 1H)	18.8 (C_5'), 25.3 (C_6'), 32.7 (C_4'), 39.6 (C_2'), 56.8 ($O\underline{C}H_3$), 98.4 ($\underline{C}H$), 109.5–136.4 (aromatic carbons),153 ($\underline{C}$=N), 160.2 ($\underline{C}$–OCH_3), 161.5 (C–NHN), 168.3 (C=O), 188.4 (C=O)	–
5b	3240 (br, NH), 3080–2820 (br, CH str.), 1710 (s, C=O),1650 (s, NH–C=O) 1602 (s),	1.48 (m, 2H, C_5'), 1.72(m, 2H, C_6'), 2.15 (m, 2H, C_4'), 2.82 (s, 2H, C_2')	2.82 (s, 1H, CH_3), 6.43 (s, 1H, CH)	6.95 (d, *J*=2 Hz, H–8), 7.42 (dd, *J*=2+7 Hz H–7), 8.12 (d, *J*=7 Hz H–5)	8.91 (s, 1H, NH),10.32(s, 1H)	–	–
5c	3210 (br, NH), 3070–2840 (br, CH str.), 1715 (s, C=O), 1665 (s, NH–C=O), 780 (C–Cl)	1.42 (m, 2H, C_5'), 1.75(m, 2H, C_6'), 2.18(m, 2H, C_4'), 2.95 (s, 2H, C_2')	–	–		–	–
5d	3260 (br, NH), 3060–3070 (br, CH str.), 1710 (s, C=O),1650 (s, NH–C=O), 1140–1120 (C–O–C)	1.52 (m, 2H, C_5'), 1.65 (m, 2H, C_6'), 2.15 (m, 2H, C_4'), 2.94 (s, 2H, C_2')	–	–	–	–	–
6a	3380–3210(br, NH), 2940–2870 (br, CH str.), 1720 (s, C=O),1650 (s, NH–C=O), 1140–1120 (C–O–C)	1.86 (m, 2H, C_9), 2.76(m, 2H, C_{10}), 2.80 (m, 2H, C_8)	3.79 (s, 3H, OCH_3)	6.98 (d, *J*=2 Hz, H–4), 7.30(dd, *J*=2+7 Hz H–2), 8.02(d, *J*=7 Hz H–1)	9.77 (s, 1H, NH),10.30 (s, 1H)	26.24 (C_9), 27 (C_{10}), 32.9 (C_8), 56.6 ($O\underline{C}H_3$), 114.1 (C_2), 121.0 (C_4, 127.1 (C_{6b}), 128.1 (C_{6a}), 134.8 (C_{11a}), 135.0 (C_{11b}), 141.3 (C_{10a}), 142.0 (C_{4a}), 159.8 ($\underline{C}$–OCH_3), 168.1 (C=O), 196.2 (C=O)	282 ([M^+] 100), 266(6.7), 247 (14.7), 239 (53.4), 216 (5.5), 171(3.4), 140 (9.3), 133 (17.2), 120 (3.6), 99 (7.6), 55 (30.2), 42 (40.5)

Table 3 *continued*

Cmpd	IR(cm^{-1})	^{1}H NMR(δ,ppm)				^{13}C NMR	
		CH_2	CH_3/OCH_3/CH	Ar–H	NH/NH_2/OH	(δ,ppm) *m/z*(%)	Mass
6b	3370–3210 (br, NH), 2920–2840 (br, CH str.), 1710 (s, C=O), 1650 (s, NH–C=O)	1.46 (m, 2H, C_9), 2.62(m, 2H, C_{10}), 2.73 (m, 2H, C_8)	2.82 (s, 1H, CH_3)	7.03(d, *J*=2 Hz, H–4), 7.23(dd, *J*=2+8 Hz H–3), 8.02 (d, *J*=7 Hz H–1)	10.27(s, 1H, NH), 1.27 (s, 1H)	–	226 ([M^+] 12), 216 (6.7), 198 (4.7), 167(1.4), 155 (0.9), 133 (17.2), 73 (100), 55 (28.2), 42 (29)
6c	3360–3220 (br, NH), 2930–2830 (br, CH str.), 1715 (s, C=O),1640 (s, NH–C=O), 775 (C–Cl)	1.72 (m, 2H, C_9), 2.65(m, 2H, C_{10}), 2.74(m, 2H, C_8)	–	6.92(d, *J*=8 Hz, H–4), 7.35(dd, *J*= 2+ 7 Hz H–2), 8.05(d, *J*= 2 Hz, H–1)	9.82 (s, 1H, NH), 10.40 (s, 1H)	–	–
6d	3370–3210 (br, NH), 2940–2820 (br, CH str.), 1710 (s, C=O), 1660 (s, NH–C=O), 1140–1120 (C–O–C)	1.65 (m, 2H, C_9), 2.52(m, 2H, C_{10}), 2.89 (m, 2H, C_8)	3.82 (s, 3H, OCH_3)	7.04(d, *J*=2 Hz, H–4), 7.25(dd, *J*=2+7 Hz H–3), 7.68 (d, *J*=7 Hz H–1)	10.15 (s, 1H, NH), 10.45 (s, 1H)	–	–
9a	3420–3020 (br NH & OH str), 2920–2850 (CH str),1740 (s, C=O, ketone), 1710 (s, C=O, acid), 1630 (s, NH–C=O), 1140–1120 (C–O–C)	1.79 (m, 2H,C_9), 2.42 (m, 2H,C_{10}), 2.75 (s, 1H,CH, C_8)	3.56 (s, 3H, OCH_3), 4.42 (d, 1H, ethanolic proton)	7.2 (d, 1H, *J*= 2 Hz, H–4), 7.42 (dd, *J*= 2+ 8 Hz, H–2),7.82 (d, 1H, *J*=8 Hz, H–1)	5.6 (s, 1H, OH), 9.02 (s, 1H, NH), 10.32 (s, 1H, NH), 11.10 (br, 1H, COOH)	22.5 (C_9), 23.4 (C_{10}), 52.4 (C_8), 56.7 ($O\underline{C}H_3$), 76.9 (OH–<u>C</u>H–COOH), 109.4–142.5 (aromatic carbons), 161.5 (<u>C</u>–OCH_3), 168.1 (C=O), 182.0 (C=O), 211.1 (C=O)	
9b	3410–3040 (br NH & OH str), 2950–2820 (CH str),1735 (s, C=O, ketone), 1705 (s, C=O, acid), 1640(s, NH–C=O), 1130–1110 (C–O–C)	1.75 (m, 2H,C_9), 2.45 (m, 2H,C_{10}), 2.83 (s, 1H,CH, C_8)	4.56 (d, 1H, ethanolic proton)	7.2 (d, 1H, *J*= 2 Hz, H–4), 7.42 (dd, *J*= 2+ 8 Hz, H–2), 7.82 (d, 1H, *J*=8 Hz, H–1)	5.6 (s, 1H, OH), 9.02 (s, 1H, NH), 10.32 (s, 1H, NH), 11.10 (br, 1H, COOH)		
10a	3380–3240 (br NH str), 2920–2860 (CH str), 1660 (s, C=O, amide), 1630 (s, NH–C=O), 1140–1120 (C–O–C)	1.48 (m, 2H,C_6), 2.72 (m, 2H,C_5)	3.62 (s, 3H, OCH_3)	7.03 (s, 1H, CH), 7.07–7.40 (m, 3H, Ar–H)	9.27 (s, 1H, NH), 10.82 (s, 1H, NH), 11.20 (s, 1H, NH)	23.0 (C_6), 38.2 (C_5), 56.9 ($O\underline{C}H_3$), 108 (C_{13a}), 110.2–137.7 (aromatic carbons), 154.6 (<u>C</u>=N), 161.5 (<u>C</u>–OCH_3), 165.2 (C=O), 167.5 (C=O)	334 [M^+] (21.9), 306 (17.2), 277 (41.1), 249 (10.4), 248 (45.2), 221 (100), 193 (10.6), 190 (15), 176 (5.7), 147 (61.2), 130 (15.5).
10b	3370–3240 (br NH str), 2930–2870 (CH str), 1650 (s, C=O, amide), 1625 (s, NH–C=O), 1130–1110 (C–O–C)	1.53 (m, 2H,C_6), 2.78 (m, 2H,C_5)	7..08 (s, 1H, CH), 7.15–7.69 (m, 3H, Ar–H)	9.35 (s, 1H, NH), 10.56 (s, 1H, NH), 11.15 (s, 1H, NH)			

(CH_2, C4'), 25.3(CH_2, C_6') and 18.8 (CH_2, C5') (Table 3) mass spectrum of **5a** molecular ion peaks was observed at 299 [M^+] (100%) corresponding to molecular weight along with some other peaks at 256 (43), 235 (4.3), 205 (23.6), 164 (4.6), 152 (18.7), 125 (16.3), 115 (13.6), 58(5.9), 42 (40.5) (Table 3).

Formation of 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*] quinoline-6,7(5*H*)-dione (**6**) involving Fischer indole cyclisation in one step instead of hydrazone in case of reaction performed using few drops of DMF from **3** is confirmed by spectral studies. ^{1}H NMR spectrum of **6a** showed absence of signals at δ 2.78 and 6.85 for methylene proton at C_2' of cyclohexanone ring and C_3 proton of quinolinone ring which were present in compound **5a** supported the formation of tittle product (**6**). ^{13}C NMR spectra also did not give any signal at δ 39.6 ppm for methylene carbon atom C_2' of cycloalkane and at 98.4 ppm for C_3 of quinolinone ring. In mass spectrum of **6a** molecular ion peaks was observed at 282 [M^+] (100%) corresponding to molecular weight along with some other peaks at 266 (6.7), 239 (53.4), 216 (5.5), 171 (3.4), 140 (9.3), 133 (17.2), 120 (3.6), 55 (30.2), 42 (40.5) (Table 3).

The neat reaction of 8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*] quinoline-6,7(5*H*)-dione (**6**) with glyoxylic acid in presence of few drops of DMF afforded the corresponding 2-hydroxy-2-(6,7-dioxo-6,7,8,9,10,11-hexahydro-5*H*-indolo[3,2-*c*] quinoline-8-yl)acetic acid (**9**).These compounds were found to be soluble in sodium bicarbonate solution with effervescences. IR spectrum of **9a** showed broad absorption bands at 3420–3020 (OH and NH stretching) along with sharp bands at 1740,1710 (both acidic and ketonic C=O), 1630 (NH–C=O), 1210 (C–O–C linkage) cm^{-1}.^{1}H NMR spectrum of **9a** showed peaks at δ 1.79 (m, 2H, CH_2; C_9), 2.42 (m, 2H, CH_2; C_{10}), 2.75 (m, 1H, CH, C_8), 4.42 (d, 1H, ethanoic proton), 5.6 (s, 1H, OH, D_2O exchangeable) and broad signal at 11.10 for OH proton of COOH, which is D_2O exchangeable. Presence of broad OH band in IR spectrum and peaks at 4.42 (ethanoic proton), 5.6 (OH proton) in ^{1}H NMR, further confirmed the formation of cycloaddition product instead of cyclocondensed product[38] as observed earlier in the reaction of glyoxylic acid with other cyclic ketones. ^{13}C NMR spectrum of **9a** showed peak at δ 22.5 (CH_2; C_9), 23.4 (CH_2; C_{10}), 52.4 (CH, C_8), 76.9 (OH–CH–COOH), 109.4–142.5 (aromatic carbons), 168.1 (NH–C=O), 182.0 and 211.1 (both C=O, acidic and ketonic) (Table 3).

Reaction of **9a** with hydrazine hydrate gave 2,7-dihydro-3*H*-pyridazino[3',4':4,5]indolo[3,2-*c*]quinoline-3,13(12*H*)-dione (**10**). These compounds were found to be insoluble in sodium bicarbonate solution showing absence of COOH group. IR spectrum of **10a** showed broad band at 3380-3240 (NH stretching) along with sharp bands at 1660, 1630 (both C=O) and 1610 (C=N) cm^{-1}. ^{1}H NMR spectrum of **10a** showed peaks δ 1.48 (m, 2H, CH_2; C_6), 2.72 (m, 2H, CH_2; C_5) and broad signals at 9.27 (s, 1H, NH), 10.82 (s, 1H, NH), 11.2 (s, 1H, NH) which are D_2O exchangeable, confirmed the formation of **10a** (Table 3). ^{13}C NMR spectrum of **10a** showed signals at δ 23.0(CH_2;C_6),38.2(CH_2;C_5),108(C_{13a}), 110.2–137.7(aromatic carbons), 154.6 (C=N), 165.2, 167.5 (both NH-C=O). In mass spectrum of **10a** molecular ion peak was observed at 334 [M^+] (21.9) corresponding to molecular weight along with some other peaks at 306 (17.2), 277 (41.1), 249 (10.4), 248 (45.2), 221 (100), 193 (10.6), 190 (15), 176 (5.7), 147 (61.2), 130 (15.5).

Experimental

Melting points were determined in open glass capillaries and were uncorrected. TLC on silica gel 'G' coated glass plates using benzene, ethanol (8: 2) as eluent was used for monitoring the progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer, ^{1}H and ^{13}C NMR spectra [$CDCl_3$ + $(CD_3)_2SO$] were taken on a Bruker –300DX spectrometer at 300 and 200 MHz respectively, using TMS as an internal standard for PMR and mass spectra were recorded on Jeol D–300 spectrometer at an ionisation potential of 70 e.v. Microwave assisted reactions were carried out on a BPL BMO model, operating at 700 W, generating 2450 MHz frequency.

(7-methoxy-2-oxo-1,2-dihydroquinolin-4-yl)hydrazine (**3a**): It was synthesised by two different ways:

(a) Conventional method: A mixture of 7-methoxy-4-hydroxy-quinoline-2(1*H*)-one (**1a**) (0.01 mol, 1.23 g) and hydrazine hydrate (15 ml) was refluxed in ethoxyethanol (30 ml) for 48 h. The reaction mass cooled to room temperature and the precipitate thus obtained was filtered and recrystallised form ethanol to give **3a.** Yield: 72%

(b) Microwave mediated synthesis: To **1a** (0.01 mol)**,** hydrazine hydrate (1.5 ml) (**2**) was added and irradiated inside microwave oven for 3 min, solid separated out was washed with water, filtered and dried which was found to be of reasonable purity (TLC) and used as such for further reaction. While for analytical and spectral studies it was recrystallised from methanol. Yield: 96%

Cyclohexane-1,3-dione (7-methoxy-2-oxo-1,2-dihydroquinolin-4-yl) hydrazone **(5a)**

(a) Conventional method: An equimolar mixture of **3a** (0.01mol) and 1,3-cyclohexanedione (**4**) (0.01mol) in 60 ml acetic acid was refluxed for 10 h. The solvent was evaporated under reduced pressure and the residue was washed with water and recrystallised with methanol to give **5a**. Yield: 60%

(b) Microwave mediated synthesis: A neat equimolar mixture (0.01 mol) of **3a** and 1,3-cyclohexanedione (**4**) in open glass vessel was placed in the microwave oven and irradiated for 5 min (TLC) at 640 W. The reaction mixture was cooled at room temperature to give solid mass, which was crystallised from ethanol and identified as **5a**. Yield: 68%

3-methoxy-8,9,10,11-tetrahydro-6H-indolo[3,2-c]quinoline-6,7(5H)-dione (**6a**)

(a) Conventional synthesis: To a mixture of acetic acid (20 ml) and conc. hydrochloric acid (5 ml) was added a solution of **5a** (299 mg, 0.01 mol) in acetic acid (15 ml) and refluxed for 7 h in an oil bath at 140°C. The reaction mixture was cooled and slowly poured into ice cold water with stirring. The solid thus obtained, was filtered and washed with 5% sodium carbonate solution (30 ml) followed by washing with water, dried and recrystallised from ethanol. Yield: 48%

(b) A solution of **3a** in 10 ml of diethylene glycol was heated at 250°C under N_2 atmosphere for 2 h. The reaction mixture was cooled and diluted with 35 ml of H_2O. The precipitate was filtered off, washed with H_2O and recrystallised from ethanol to give **6a.** Yield : 52%

(c) A solution of **5a** in polyphosphoric acid (5 ml) in presence of anhydrous aluminum trichloride (Al_2Cl_3) (2mg) is heated on an oil bath at 140–150°C for 4 h., poured in to crushed ice. The precipitate was filtered off, washed with H_2O and recrystallised from methanol gave **6a.** Yield : 42%

(b) Microwave mediated synthesis: The reaction was studied under different conditions to optimise the best process.

(a) Neat + few drops of DMF: An equimolar mixture (0.01mol) of **3a** and 1,3-cyclohexanedione (**4**) with 2–3 drops of DMF, in open glass vessel was irradiated inside a microwave oven at 640 W for appropriate time (TLC). On cooling solid mass separated out, which was washed with water and found to be pure by TLC. For analytical and spectral data **6a** was recrystallised from methanol. Yield: 85%

(b) Using montmorillonite KSF as solid acid: **3a** and 1,3-cyclohexanedione (**4**) (0.01 mol) was dissolved in minimum amount of methanol (5 ml) and to this solution, montmorillonite KSF (80 % by weight of reactants) was added. The mixture was swirled for a while followed by removal of solvent under gentle vacuum. The dry powder thus obtained was irradiated in a microwave oven for an appropriate time (TLC) (Table 2). The product was eluted with methanol and solvent was evaporated under rotoevaporator give solid mass, which was recrystallised from methanol to give compound identified as **5a**. **5a** was again adsorbed on montmorillonite KSF and irradiated for an appropriate time to gave 3-methoxy-8,9,10,11-tetrahydro-6*H*-indolo[3,2-*c*]quinoline-6,7(5*H*)-dione (**6a**) in lower yield. Yield: 76%

Remaining compounds listed in Table 2 were synthesised following same procedure using few drops of DMF.

2-hydroxy-2-(3-methoxy-6,7-dioxo-6,7,8,9,10,11-hexahydro-5H-indolo[3,2-c]quinoline-8-yl)acetic acid (**9a**)

(a) Conventional method: A mixture of **6a** (2.52 g, 0.01mol) and **7** (1.72 g, 0.01mol) was refluxed in DMF (50 ml) in presence of potassium hydroxide (two pellets) for 10 h. On cooling reaction mixture was poured on ice cold HCl solution. The solid thus obtained was filtered, washed well with water and recrystallised from methanol to give **9a**. Yield: 62%

(b) Microwave mediated synthesis: An equimolar neat mixture (0.01mol) of **6a** and **7** with 2–3 drops of DMF, in open borosil vessel was irradiated inside a microwave oven at 640 W for appropriate time (TLC). On cooling solid mass separated out, was washed with water and found to be pure by TLC and used as such for further reaction. Yield: 85%

For analytical and spectral studies it was recrystallised from methanol.

10-methoxy-2,7-dihydro-3H-pyridazino[3',4':4,5]indolo[3,2-c] quinoline-3,13(12H)-dione (**10a**)

(a) Conventional synthesis: A solution of **9a** (3.55 g, 0.01mol) and hydrazine hydrate (70–80 ml) was refluxed for 52 h. The reaction mixture was cooled to room temperature and solid separated, washed with water, dried and recrystallised from methanol to give **10a.** Yield: 40%

(b) Microwave mediated synthesis: A neat mixture of **9a** (355 mg, 0.01mol) and hydrazine hydrate (1.5 ml) was irradiated inside microwave oven till completion of the reaction (TLC). On cooling solid separated, which was filtered, washed with water and found to be of reasonable purity (TLC). For analytical and spectral data **10a** was recrystallised from methanol. Yield: 88%

Identity of compounds synthesised by various methods was established on the basis of mixed m.p.s and spectral studies.

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