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p-Toluene sulfonic acid- catalysed one pot synthesis, anxiolytic activity and molecular docking studies of indeno[1,2-b]quinolines derivatives.

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ABSTRACT

A simple, straightforward and versatile multicomponent synthetic protocol for indeno-fused heterocycles indeno[1,2-b]quinoline derivatives has been developed. The strategy involves the one pot three component reaction of 1,3-indanedione, aryl-aldehyde, enaminone, by p- toluene sulphonic acid (10 mol%) in ethanol under reflux in good yield. The chemical structures of the compounds were proved by IR, ^{1}H NMR, and Mass spectrometric data and CHN analysis. Moreover, the antianxiety activity of the newly synthesized compounds (6a-f) was investigated by the elevated plus maze method. Derivatives 6a, 6b, 6d and 6k found to be most potent among the series and exhibited significant anxiolytic activity ($^{***}P < 0.001$). The molecular modeling studies also predicted good binding interactions of most active molecules with the Serotonin 5-HT$_{2A}$ receptor.

Keywords: indeno[1,2-b]quinoline-9,11(6H,10H)-dione, multicomponent reactions (MCR), 1-4 dihydropyridine (1-4 DHP), *p*-Toluene sulfonic acid (p-TsOH), Elevated plus-maze, molecular docking.

INTRODUCTION

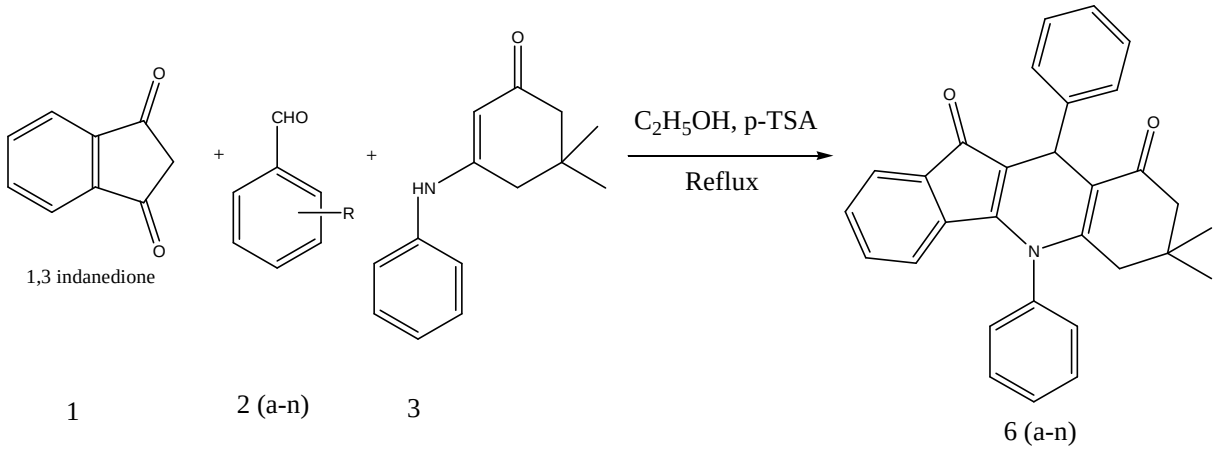
The development of novel and improved synthetic methodologies for the construction of potentially bioactive compounds represent a major challenge for the chemist in organic synthesis. Many biologically important molecular scaffolds can be efficiently synthesized from readily available starting materials with the help of Multicomponent reactions (MCR). Multi component reactions (MCR) allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the construction of molecular diversity and complexity. They also have considerable advantages in terms of user and environmental friendliness because of the step reduction and atom economy related to their use[1]. They have inherent advantage over conventional two component reactions in several aspects: operational simplicity, convergence, facile one pot operation. These reactions surpass time consuming and costly process of purification of various precursors and isolation of intermediate, minimized waste generation and producing the transformation green. Henceforth search and discovery for new MCRs, along with full exploitation of the already known MCRs are of considerable interest[2].

There are numerous methods available for the synthesis of 1-4 dihydropyridine (1-4 DHP) bearing polyhydroquinolines. The classical method involves the three component condensation of an aldehyde with ethyl-acetoacetate, and ammonia in acetic acid or refluxing alcohol[3]. Recently several new methodologies have been reported for the synthesis of polyhydroquinolines including use of $(YbOTf)_3$ as catalyst[4], $(ScOTf)_3$[5], HClO4-SiO2[6], l-proline[7], bakers yeast [8], organocatalyst[9], *p*-toluene-sulphonic acid[10], ZnO[11], Ni-nanoparticles[12], PPA-SiO_2 [13], microwave[14], $Cs_{2.5}H_{0.5}PW_{12}O_{40}$[15], FeF_3[16], TiO_2 nanoparticles[17]. These methods have their own merits and shortcoming.

With a 1-4 dihydropyridine (1-4,DHP) parent nucleus, indenoquonoline derivatives have shown a diverse range of biological activities such as 5-HT receptor binding[18], antitumor activity[19-20] cytotoxic activity[21] actylcholinesterase inhibitor[22], antimalarials[23], anti-inflammatory activity[24], new topo I/II inhibitors[25], DNA intercalation[26], antiploriferative[27], anti-mycobacterial[28], antihyperglycemic and lipid modulating[29]. Owing to these diverse biological activities, these compounds have distinguished themselves as a hetrocycles of profound biological significance.

Many of the reported methods are associated with several shortcomings such as long reaction time, expensive catalyst, harsh reaction conditions, tedious work up procedures, use of expensive column chromatography, low product yields and large quantity of volatile organic solvents. Further the high cost of most conventional room temperature ionic liquids[30] and apprehension regarding their toxicity inspired us to explore other clean method having operational simplicity, economic viability and mild reaction conditions.

p-Toluene sulfonic acid (*p*-TsOH), an readily available and cheap reagent has been used as an acidic catalyst in the synthesis of a variety of heterocyclic compounds[31]. However, the use *p*- TsOH as a catalyst in ethanolic media for the synthesis of poly-substituted indeno[1,2-*b*]quinolines and their derivatives has not been reported. In this communication, we wish to report a general and highly efficient synthesis of poly-substituted indeno[1,2-*b*]quinolines, using *p*-TsOH as a catalyst, from various enaminones under refluxing condition. This is an efficient synthesis which not only preserves the simplicity of the reaction but also consistently gives the corresponding products in good to excellent yields (Scheme 1).



Scheme 1 Synthetic route to indeno[1,2-*b*]quinoline derivatives

MATERIALS AND METHODS

2. Experimental

2.1 Material and methods

The chemicals and reagents used from various chemical companies like Alfa-Aesar, HiMedia, Merck India and CDH and were used without purification. Enaminones were prepared according to the standard literature procedures. The progress of the reaction was monitored by thin layer chromatography (TLC- ethyl acetate: n-hexane- 1:3) using pre-coated silica gel G plates using UV chamber for visualization of TLC spots. IR spectra were recorded on Shimadzu FT-IR spectrophotometer using KBr pellets. Band positions are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were obtained using on Bruker's AVANCE-III 400MHz FT NMR spectrometers by using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in parts per

million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (J) are reported in hertz (Hz), and spin multiplicities are represented by the symbols s (singlet), d (doublet), t (triplet), q (quartet), dt (doublet of triplet) and m (multiplet). Mass spectra were determined on Applied Biosystems 3200 Q Trap LC/MS/MS instrument.

2.3. Chemistry

2.4 General experimental procedure for the synthesis of 7,7-dimethyl-5,10-diphenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione 6 (a-n)

A mixture containing 1,3-indanedione **1** (1 mmol) aryl-aldehyde **2** (1 mmol), enaminone **3a** (1 mmol), p- toluene sulphonic acid (10 mol%) and ethanol (5.0 mL) was introduced into a 50 mL flask and the mixture was refluxed for the designated time until the reaction was completed (monitored by TLC). The resulting red colored solid product was filtered, treated with water and followed by brine solution and extracted by ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness to give crude product. The pure product was obtained by recrystallization from methanol.

Table No 1 The Synthesis of 5H-indeno[1,2-b]quinoline derivatives 6(a-n)

Entry	R	Product
1	H	6a
2	o-Cl	6b
3	m-Cl	6c
4	p-Cl	6d
5	,4-Cl_2	6e
6	o-OH	6f
7	p-OH	6g
8	p-OCH_3	6h
9	3-OCH_3-4OH	6i
10	p-NO_2	6j
11	o-NO_2	6k
12	3,4-$(OCH_3)_2$	6l
13	p-$(CH_3)_2NH_2$	6m
14	o-furfuryl	6n

2.5 The spectroscopic and analytical data for the synthesized compounds are presented below

2.5.1. 7,7-dimethyl-5,10-diphenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6a)

Red crystals; m.p. 255-256^0 C; IR (KBr. υ, cm^{-1}): 3060, 2958, 1715, 1680, 1650, 1625, 1556, 1510, 1453, 1396, 1360, 1300, 1250, 1186, 1138, 1100, 1010, 884, 770, 722, 680; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.892 (s, 3H, CH_3), 0.992 (s, 3H, CH_3), 2.012-2.267 (m, 4H, 2x CH_2), 5.111 (s, 1H, CH), 5.133-5.152 (d, 1H, ArH, J=7.6 Hz), 6.795-6.883 (t, 1H, ArH, J=7.6 Hz), 7.035-7.071 (t, 1H, ArH, J= 7.6Hz), 7.115-7.133 (d, 1H, ArH, J= 18Hz), 7.235-7.290 (q, 3H, ArH, J=7.2 Hz), 7.426-7.443 (d, 4H, ArH, J= 6.8 Hz), 7.583-7.649 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{25}NO_2$: C, 83.5; H, 5.84; N, 3.25 %. Found: C, 83.07, H, 5.78; N, 3.21%.

2.5.2. 10-(2-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6b)

Red crystals; m.p. 230-232^0 C; IR (KBr. υ, cm^{-1}): 3362, 3060, 2960, 1685, 1625, 1585, 1560, 1455, 1388, 1310, 1250, 1225, 1170, 1035, 886, 830, 749, 696; ^{1}HNMR (400 MHz , $CDCl_3$): δ**:** 0.908 (s, 3H, CH_3), 0.973 (s, 3H, CH_3), 1.990-2.306 (m, 4H, CH_2), 5.082-5.100 (d, 1H ArH, J= 7.2 Hz), 5.391(s, 1H, CH), 6.790-6.830 (dt, 1H, ArH, J= 7.6 Hz), 7.033-7.086 (m, 2H ArH), 7.172-7.212 (dt, 1H, ArH, J=7.6 Hz), 7.261-7.268 (d, 3H, ArH, J= 2.8 Hz), 7.445 (s, 1H, ArH), 7.532-7.554 (dd, 1H, ArH, J= 7.6 Hz), 7.577-7.647 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{24}ClNO_2$: C, 77.33; H, 5.14; N, 2.98 %. Found: C, 76.89; H, 5.14; N, 2.98 %.

2.5.3. 10-(3-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6c)

Red crystals; m.p. 218-220^0 C; IR (KBr. υ, cm^{-1}): 3060, 2954, 1680, 1650, 1580, 1560, 1508, 1450, 1390, 1300, 1250, 1170, 1140, 1052, 885, 840, 765, 730, 680. ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.906 (s, 3H, CH_3), 0.997 (s, 3H, CH_3), 2.026-2.270 (m, 4H, 2x CH_2), 5.087 (s, 1H, CH), 5.147-5.166 (d, 1H, ArH J=7.6 Hz), 6.815-6.854 (t, 1H, ArH, J= 7.6 Hz), 7.057-7.102 (m, 2H, ArH), 7.170-7.208 (t, 1H, ArH, J= 7.6Hz), 7.290-7.307 (d, 1H, ArH, J= 6.8 Hz), 7.353-7.384 (m, 2H, ArH), 7.432-7.447 (d, 2H, ArH, J= 6Hz), 7.593-7.659 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{24}ClNO_2$: C, 77.33; H, 5.14; N, 2.98 %. Found: C, 76.88; H, 5.14; N, 2.97 %.

2.5.4. 10-(4-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6d)
Red crystals; m.p. 218-220^0 C; IR (KBr. υ, cm^{-1}): 3060, 2950, 2870, 1715, 1680, 1632, 1550, 1510, 1450, 1400, 1360, 1298, 1251, 1224, 1190, 1170, 1100, 1010, 880, 840, 764, 698. ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.876 (s, 3H, CH_3), 0.983 (s, 3H, CH_3), 1.986-2.303 (m, 4H, ArH), 5.072 (s, 1H, CH), 5.130-5.149 (d, 1H, ArH, J= 7.6 Hz), 6.804-6.841 (t, 1H, ArH, J= 7.2 Hz), 7.044-7.081 (t, 1H, ArH, J= 7.2 Hz), 7.200-7.221 (d, 2H, ArH, J= 8.4 Hz), 7.373-7.290 (d, 1H, ArH, J=6.8 Hz), 7.352-7.373 (d, 2H, ArH, J= 8.4Hz), 7.417-7.435 (d, 2H, ArH, J= 7.2 Hz), 7.583-7.651 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{24}ClNO_2$: C, 77.33; H, 5.14; N, 2.98 %. Found: C, 76.88; H; 5.13; N, 2.98 %.

2.5.5. 10-(3,4-dichlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6e)
Red crystals; m.p. 281-283^0 C; IR (KBr. υ, cm^{-1}): 3076, 2926, 2850, 1682, 1634, 1590, 1560, 1460, 1360, 1294, 1274, 1221, 1190, 1140, 1060, 1028, 944, 888, 839, 735, 720, 684; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.906 (s, 3H, CH_3), 0.997 (s, 3H, CH_3), 2.025-2.270 (m, 4H, 2x CH_2), 5.062 (s, 1H, CH), 5.152-5.171 (d, 1H, ArH, J=7.6 Hz), 6.826-6.863 (t, 1H , ArH, J= 7.2 Hz), 7.069-7.106 (t, 1H, ArH, J= 7.2 Hz), 7.298-7.325 (m, 3H, ArH), 7.421-7.454 (t, 3H, ArH, J= 7.2 Hz), 7.598-7.665 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{23}Cl_2NO_2$: C, 72.00; H, 4.63; N, 2.80 %. Found: C, 71.58; H, 4.58; N, 2.80 %. Found: C, 71.58; H, 4.58; N, 2.8%.

2.5.6. 10-(2-hydroxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6f)
Red crystals; m.p. >300^0 C; IR (KBr. υ, cm^{-1}): 3392, 2950, 1682, 1652, 1587, 1550, 1450, 1390, 1360, 1290, 1255, 1221, 1190, 1162, 1100, 1018, 955, 938, 888, 832, 705, 670.
^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.824 (s, 3H, CH_3), 0.992 (s, 3H, CH_3), 2.476-2.586 (m, 4H, 2x CH_2), 5.234 (s, 1H, CH), 5.333-5.352 (d, 1H, ArH, J= 7.6 Hz), 6.882-6.918 (m, 1H, ArH), 7.098-7.414 (m, 1H, ArH), 7.230-7.267 (m, 1H, ArH), 7.301-7.326 (t, 2H, ArH, J=5.2 Hz), 7.345-7.387 (t, 2H, ArH, J=7.6 Hz), 7.428-7.448 (d, 3H, ArH, J= 8 Hz), 7.580-7.602 (dd, 2H, ArH, J= 7.6 Hz), 9.346 (s, 1H, OH); Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63; N, 3.13%. Found: C, 80.09; H, 5.57; N, 3.09 %.

2.5.7. 10-(4-hydroxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6g)
Red crystals; m.p. >300^0 C; IR (KBr. υ, cm^{-1}): 3250, 2956, 1680, 1666, 1584, 1454, 1430, 1395, 1300, 1225, 1185, 1152, 1060, 1006, 942, 850, 766, 730, 700; ^{1}HNMR (400 MHz , $CDCl_3$): **δ:** 0.887 (s, 3H, CH_3), 0.985 (s, 3H, CH_3), 1.998-2.265 (m, 4H, ArH, 2x CH_2), 5.044 (s, 1H, CH), 5.125-5.143 (d, 1H, ArH, J=7.2 Hz), 5.228 (s, 1H, OH), 6.667-6.688 (d, 2H, ArH, J= 8.4 Hz), 6.795-6.833 (t, 1H, ArH, J= 7.6 Hz), 7.036-7.073 (t, 1H, ArH, J= 7.6 Hz), 7.263-7.294 (m, 3H, ArH), 7.428-7.445 (d, 2H, ArH, J= 6.8 Hz), 7.581-7.646 (m, 3H, ArH); Anal. Calcd. for $C_{30}H_{25}NO_3$: C, 80.51; H, 5.63; N, 3.13%. Found: C, 80.09; H, 5.58; N, 3.1 %.

2.5.8. 10-(4-methoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6h)
Red crystals; m.p. 252-254^0 C; IR (KBr. υ, cm^{-1}): 2960, 1686, 1628, 1588, 1555, 1510, 1455, 1392, 1362, 1250, 1222, 1180, 1170, 1138, 1032, 834, 760, 707; ^{1}HNMR (400 MHz , $CDCl_3$): δ**:** 0.905 (s, 3H, CH_3), 1.002 (s, 3H, CH_3), 2.013-2.277 (m, 4H, 2x CH_2), 3.747 (s, 3H, OCH_3), 5.076 (s, 1H, CH), 5.141-5.159 (d, 1H, ArH, J= 7.2 Hz), 6.802-8.845 (t, 3H, ArH, J= 8.4Hz), 7.048-7.085 (t, 1H, ArH, J= 7.2 Hz), 7.286-7.304 (d, 1H, ArH, J= 7.2 Hz), 7.352-7.374 (d, 2H, ArH, J= 8.8 Hz), 7.443-7.461 (d, 2H, ArH, J= 7.2 Hz), 7.594-7.660 (dt, 3H, ArH, J=13.2 Hz). Anal. Calcd. for $C_{31}H_{27}NO_3$: C, 80.67; H, 5.9; N, 3.03%. Found: C, 80.23; H; 5.84, N, 3.00%.

2.5.9. 10-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6i)
Red crystals; m.p. 270-272^0 C; IR (KBr. υ, cm^{-1}): 3064, 2954, 2870, 1682, 1630, 1556, 1456, 1390, 1362, 1170, 1102, 1026, 885, 758; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.913 (s, 3H, CH_3), 0.994 (s, 3H, CH_3), 2.003-2.273 (m, 4H, 2x CH_2), 3.927(s, 3H, OCH_3), 5.025 (s, 1H, CH), 5.126-5.144 (d, 1H, ArH, J=7.2 Hz), 5.445 (s, 1H, OH), 6.744-6.814 (m, 3H, ArH), 7.055 (s, 1H, ArH), 7.139 (s, 1H, ArH),7.278, 7.295 (d, 1H, ArH, J=6.8 Hz), 7.412-7.429 (d, 1H, ArH, J=6.8 Hz), 7.525-7.542 (d, 1H, ArH, J=6.8 Hz), 7.575-7.643 (m, 2H, ArH); Anal. Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93%. Found: C, 77.55; H, 5.65; N, 2.93%.

2.5.10. 7,7-dimethyl-10-(4-nitrophenyl)-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6j)
Red crystals; m.p. 248-250^0 C; IR (KBr. υ, cm^{-1}): 2954, 1680, 1634, 1590, 1452, 1394, 1294, 1226, 1064, 1020, 830, 705; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.883 (s, 3H, CH_3), 0.970 (s, 3H, CH_3), 2.108-2.152 (d, 1H, CH_2, J=17.6 Hz), 2.256-2.372 (m, 3H, CH_2), 5.064 (s, 1H, CH), 5.238-5.254 (d, 1H, ArH, J=6.4 Hz), 7.039-7.055 (d, 2H, ArH, J=6.4 Hz), 7.091 (s, 2H, ArH), 7.305 (s, 2H, ArH), 7.496-7.554 (m, 3H, ArH), 7.586-7.636 (m, 4H, ArH); Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88%. Found: C, 75.19, H, 5.02; N, 5.85%.

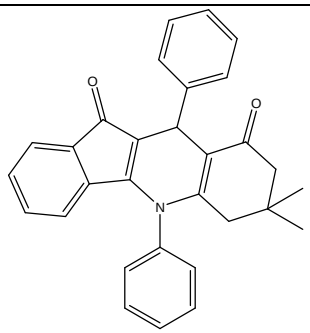
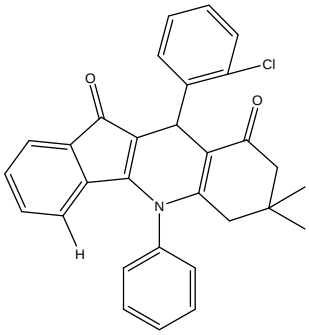
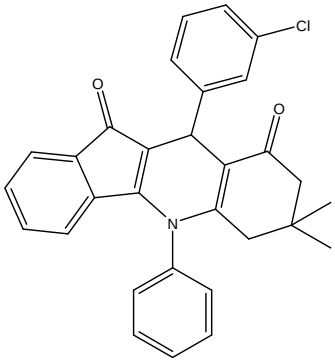
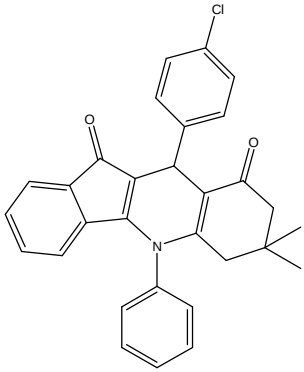
2.5.11. 7,7-dimethyl-10-(2-nitrophenyl)-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6k)
Red crystals; m.p. 240-241^0 C; IR (KBr. υ, cm^{-1}): 3060, 2951, 1680, 1632, 1562, 1452, 1399, 1294, 1245, 1168, 1102, 1029, 888, 845, 760; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.883 (s, 3H, CH_3), 0.970 (s, 3H, CH_3), 2.063- 2.171 (m, 4H, 2x CH_2), 5.117-5.136 (d, 1H, ArH, J=7.6 Hz), 5.695 (s, 1H, CH), 6.814-6.854 (td, 1H, ArH, 7.6 Hz), 7.055-7.092 (t, 1H, ArH, J=7.2 Hz), 7.294-7.284 (m, 2H, ArH), 7.390-7.497 (m, 2H, ArH), 7.582-7.715 (m, 3H, ArH), 7.801-7.939 (m, 3H, ArH) M.S: m/z = 477.4 (M^+1); Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88%. Found: C, 75.17; H, 5.03; N, 5.84%.

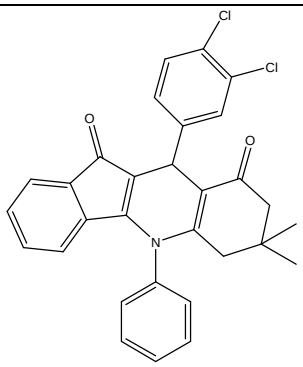
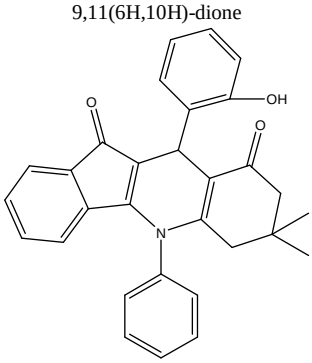
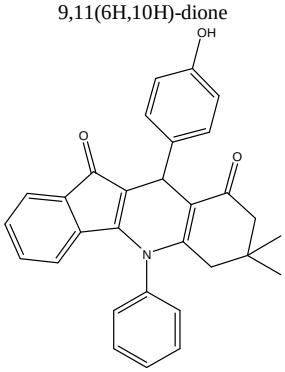
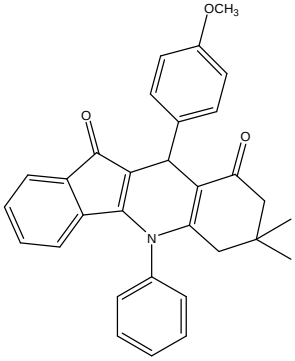
2.5.12. 10-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6l)
Red crystals; m.p. 288-290^0 C; IR (KBr. υ, cm^{-1}): 2955, 2928, 1682, 1630, 1590, 1555, 1452, 1392, 1299, 1252, 1140, 1056, 1028, 976, 928, 766; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.923 (s, 3H, CH_3), 0.999 (s, 3H, CH_3), 2.153-2.241 (m, 4H, 2x CH_2), 3.792 (s, 3H, OCH_3), 3.898 (s, 3H, OCH_3), 5.062 (s, 1H, CH), 5.123-5.142 (d, 1H, ArH, J=7.6 Hz), 7.070-7.098 (m, 3H, ArH), 7.284-7.301 (d, 2H, ArH, J=6.8 Hz), 7.406-7.424 (d, 3H, ArH, J=7.2 Hz), 7.577-7.664 (m, 4H, ArH); **M.S:** m/z = 492.3 (M^+1) Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; N, 2.85%. Found: C, 77.75; H, 5.89; N, 2.82%.

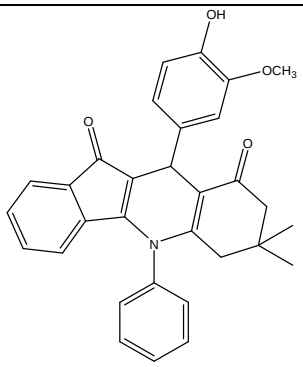
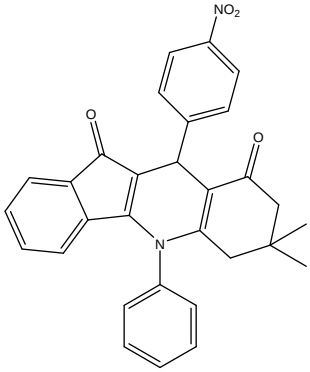
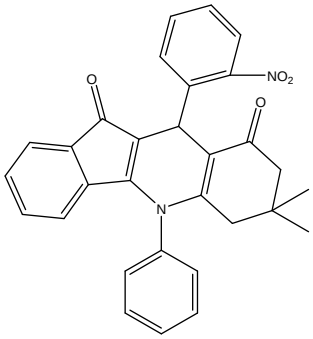
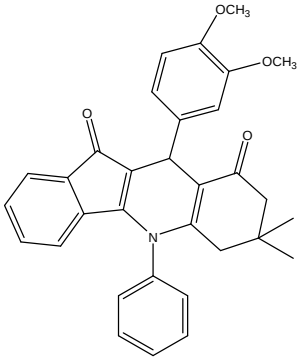
2.5.13. 10-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6m)
Red crystals; m.p. 260-262^0 C; IR (KBr. υ, cm^{-1}): 3061, 2959, 2870, 1652, 1630, 1510, 1366, 1250, 1101, 990, 886, 818, 720; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.892(s, 3H, CH_3), 0.992 (s, 3H, CH_3), 2.154-2.267 (m, 2H, 2x CH_2), 3.135 (s, 6H, $N(CH_3)_2$), 5.101 (s, 1H, CH), 5.342-5.361 (d, 1H, ArH, J=7.6 Hz), 6.718-6.741 (d, 1H, ArH, J=9.2 Hz), 6.952-6.975 (d, 1H, ArH, J=9.2 Hz), 7.381 (s, 2H, ArH), 7.692-7.712 (t, 3H, ArH, J=4Hz), 7.772 (s, 2H, ArH), 7.900-7.904 (d, 2H, ArH, J= 1.6 Hz); M.S: m/z = 474.4 (M^+); Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.9%. Found: C, 80.55; H, 6.31; N, 5.86 %.

2.5.14. 10-(fura5n-2-yl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione (6n)
Red crystals; m.p. 205-207^0 C; IR (KBr. υ, cm^{-1}): 2952, 1684, 1584, 1560, 1510, 1455, 1390, 1300, 1220, 1170, 1102, 1060, 1016, 886, 824, 768, 734; ^{1}HNMR (400 MHz , $CDCl_3$): δ: 0.914 (s, 3H, CH_3), 0.995 (s, 3H, CH_3), 1.979-2.252 (m, 4H, 2x CH_2), 5.166- 5.185 (d, 1H, ArH, J= 7.6 Hz), 5.281 (s, 1H, CH), 6.218-6.249 (m, 2H, furyl-H), 6.812-6.850 (td, 1H, ArH,J=7.2 Hz), 7.061-7.089 (t, 1H, ArH, J= 7.2 Hz), 7.213 (s, 1H, ArH), 7.330-7.347 (d, 1H, furyl-H, J=6.8 Hz), 7.442 (s, 2H, ArH), 7.561-7.633 (m, 3H, ArH); Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32%. Found: C, 79.35, H, 5.45, N, 3.28%.

Table No 2 The experimental details of 5H-indeno[1,2-b]quinoline derivatives 6(a-n)

S. No	Product	Structure	Time (hr.)	Yield (%)	m. p. (^{0}C)
1	6a	 7,7-dimethyl-5,10-diphenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	3.0	78	255-256
2	6b	 10-(2-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	2.0	81	230-232
3	6c	 10-(3-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	2.0	73	218-220
4	6d	 10-(4-chlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	2.5	85	234-236

5	6e	 10-(3,4-dichlorophenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	1.5	83	281-283
6	6f	 10-(2-hydroxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	4.5	71	>300
7	6g	 10-(4-hydroxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	4.5	70	>300
8	6h	 10-(4-methoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	4.0	75	252-254

9	6i	 10-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	3.5	78	270-272
10	6j	 7,7-dimethyl-10-(4-nitrophenyl)-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	2.5	82	248-250
11	6k	 7,7-dimethyl-10-(2-nitrophenyl)-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	2.5	80	240-241
12	6l	 10-(3,4-dimethoxyphenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	4.0	77	288-290

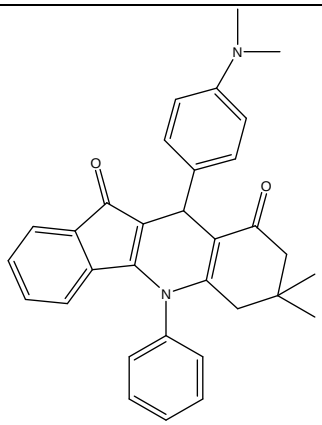
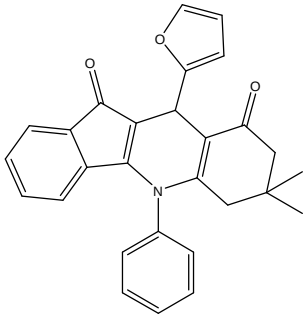
13	6m	 10-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	3.0	77	260-262
14	6n	 10-(furan-2-yl)-7,7-dimethyl-5-phenyl-7,8-dihydro-5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione	3.0	76	205-207

Table No 3 IR Absorption frequencies of synthesized derivatives (6a-n) in cm^{-1}

Entry	C-H str (Ar)	C-H str (CH_3)	C=O str	C=C str (Ar)	C-N str	C-H def (Ar)	C-Cl str	O-H str	C-O str	C-O-C str	N-H str	N=O str
6a	3062	2956, 2872	1687	1631,1587, 1452	1365	855	-	-	-	-	-	-
6b	3062	2956, 2924	1685	1631,1580, 1490	1361	889	698	-	-	-	-	-
6c	3064	2956, 2868	1687	1633,15871452	1363	885	709	-	-	-	-	-
6d	3057	2956, 2870	1685	1631,15871489	1363	887	696	-	-	-	-	-
6e	3059	2953, 2872	1685	1629,15851454	1361	887	698	-	-	-	-	-
6f	3060	2948, 2867	1684	1630,15861455	1363	885	-	3260	1190	-	-	-
6g	3059	2914, 2846	1685	1629,15871456	1363	885	-	3255	1184	-	-	-
6h	3062	2958, 2897	1685	1639,15851508,1454	1363	885	-	-	-	1255, 1031	-	-
6i	3064	2924	1685	1629,1587 1512,1452	1363	885	-	3250	1168	1255, 1031	-	-
6j	3084	2930, 2874	1686	1630,15851520	1360	887	-	-	-	-	-	1558, 1394
6k	3082	2926, 2872	1687	1629,15871525	1359	887	-	-	-	-	-	1556, 1390
6l	3080	2954, 2872	1685	1629,15871512,1450	1361	887	-	-	-	1224, 1026	-	-
6m	3078	2926, 2870	1685	1629,15871514,1454	1365	889	-	-	-	-	3354	-
6n	3053	2956, 2872	1685	1633,15871525,1454	1361	887	-	-	-	1222, 1016	-	-

2.6 Pharmacology

The experimental animals were swiss albino mice (20-25 gm) of either sex used. They were housed in groups in polypropylene cages with wood shavings as bedding, under a controlled 12 h/12 h light/dark cycle (lights on at 7:00 a.m.) and controlled temperature. The animals were given standard laboratory feed and water *ad- libitum* with the exception of 1 h before and during the experiments. The experiments were performed between 8.00 am to 1.00 pm. Concentration of each compound (40 mg/kg) was used in the form of freshly prepared suspensions in 1% tween 80. All solutions were prepared freshly on test days and given intraperitoneally (i.p.) in a volume of 0.5 ml/20g body weight of mice. The experimental animals were treated with fluoxetine (40 mg/ kg, n =3), or the compounds (40

mg/kg) 60 min before evaluation in the maze. The control group was given saline with 1% tween 80. The experiments were conducted in a sound proof laboratory. All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee.

2.6.1. Anxiolytic activity

The Elevated plus-maze comprised of two open (25cm × 5 cm) and two enclosed (25cm × 5 cm×16 cm) arms that radiated from the central platform (5cm × 5 cm) to form a plus sign. The maze was constructed of black acrylic sheet. The plus maze was elevated to a height of 50 cm above from the floor level by a single central. Thirty min after i.p. administration of the test drug or the standard the trial was started by placing an animal on the central platform of the maze facing an open arm. During the 5 min experiment, behavior of mice was recorded as (i) preference of the mice for its first entry into the open and closed arms, and (ii) the numbers of entries into the open or closed arms. The mice were considered to have entered an arm when all four paws were on the arm. The apparatus was cleaned thoroughly between trials with damp and dry towels. All behavioral recording were carried out with the observer unaware of the treatment of the mice had received. The results of EPM have been summarized in Table No 4.

Table No 4 Antianxiety activity of the synthesized compounds in elevated plus maze

Group	Number of open arm entries	Number of close arm entries
Control	2.33 ± 0.33	4.36 ± 0.13
Fluoxetine	8.33 ± 1.20***	1.33 ± 0.11
6a	7.33 ± 0.33***	1.50 ± 0.79
6b	8.33 ± 0.33***	1.89 ± 0.56
6c	6.0 ± 0.58**	1.06 ± 0.22
6d	7.67 ± 0.33***	1.03 ± 0.11
6e	5.03 ± 1.07**	1.79 ± 0.23
6f	4.0 ± 0.58ns	1.98 ± 0.10
6g	3.67 ± 0.88ns	1.79 ± 0.45
6h	5.33 ± 0.33*	1.65 ± 0.37
6i	5.67 ± 0.88*	1.59 ± 0.47
6j	6.67 ± 0.67**	5. 68 ± 0.25
6k	7.33 ± 0.33***	1.00 ± 0.29
6l	5.33 ± 0.88*	1.46 ± 0.13
6m	3.33 ± 0.67ns	1.00 ± 0.19
6n	3.0 ± 1.0ns	2.45 ± 0.47

*Values represent means ±S.E.M. (n =3). *P < 0.05, ** P< 0.01, ***P < 0.001 compared with vehicle (One-way ANOVA followed by Dunnett's post hoc test).*

Test compounds were administered at 40 mg/kg, fluoxetine was administered at 40 mg/kg

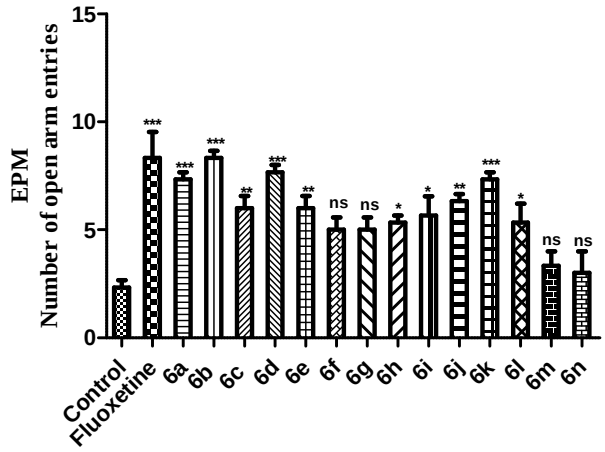


Fig 1: Effects of different synthesized derivatives (6a-n) in elevated plus maze test in mice. Results are expressed as means ± S.E.M. (n =3). *P < 0.05, **P < 0.01, ***P < 0.001 compared with vehicle-treated animals

2.6.2 Neurotoxicity screening (NT)

The neurotoxicity of the compounds was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Trained mice were given an intraperitoneal injection

of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1min in each of the trials. The results are shown in Table No. 5

Table No. 5 Neurotoxicity screening of the synthesized compounds in rotarod test

Groups	Rota rod test
Control	_
Fluoxetine	_
6a	0/4
6b	0/4
6c	0/4
6d	0/4
6e	0/4
6f	0/4
6g	0/4
6h	0/4
6i	0/ 4
6j	0/4
6k	0/4
6l	0/4
6m	0/4
6n	0/4

Rotarod toxicity (number of animals exhibiting toxicity/number of animals tested).
Compounds prepared were administered at 40 mg/kg; fluoxetine was administered at 40 mg/kg.

2.6.3. Statistical analysis

Results are expressed as mean SEM; n represents the number of animals. Data obtained from pharmacological experiments were analyzed by one way analysis of variance (ANOVA) followed by Dunnet's test and used to evaluate the results, using GraphPad Prism version 5.02. A p-value of less than 0.05 was considered statistically significant.

2.6.4. Docking study

The docking analysis of all molecule was performed using Maestro, version 9.0 implemented from Schrodinger molecular modeling suite. The molecules were sketched in the 3D format using build panel and LigPrep module was used to produce low-energy conformers. The crystal structures of Serotonin 5-HT_{2A} receptor (PDB ID: 2VT4) retrieved from Protein Data Bank (www.rcsb.org). The protein was prepared by giving preliminary treatment like adding hydrogen, adding missing residues, refining the loop with prime and finally minimized by using OPLS- 2005 force field. Grid for molecular docking was generated with bound co-crystallized ligand. Molecules were docked using Glide in standard precision mode, with up to three poses saved. Ligands were kept flexible by producing the ring conformations and by penalizing non-polar amide bond conformations, whereas the receptor was kept rigid throughout the docking studies. All other parameters of the Glide module were maintained at their default values. The lowest energy conformation was selected for the prediction of ligand interactions with the active sites of Serotonin 5-HT_{2A} receptor.

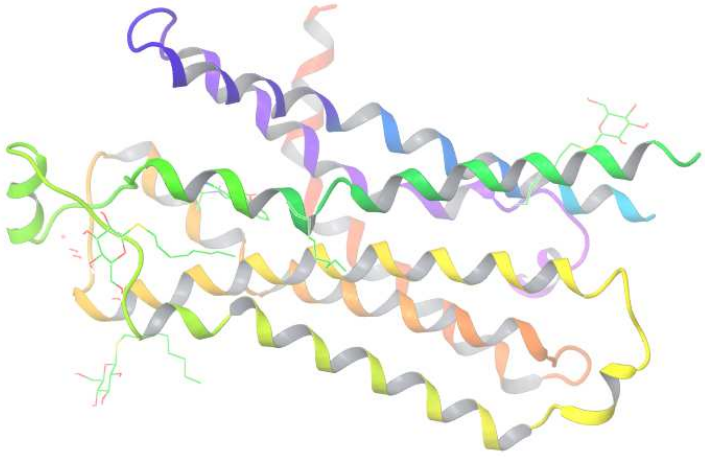


Fig 2: Structure of Serotonin 5-HT_{2A} receptor (PDB ID: 2VT4)

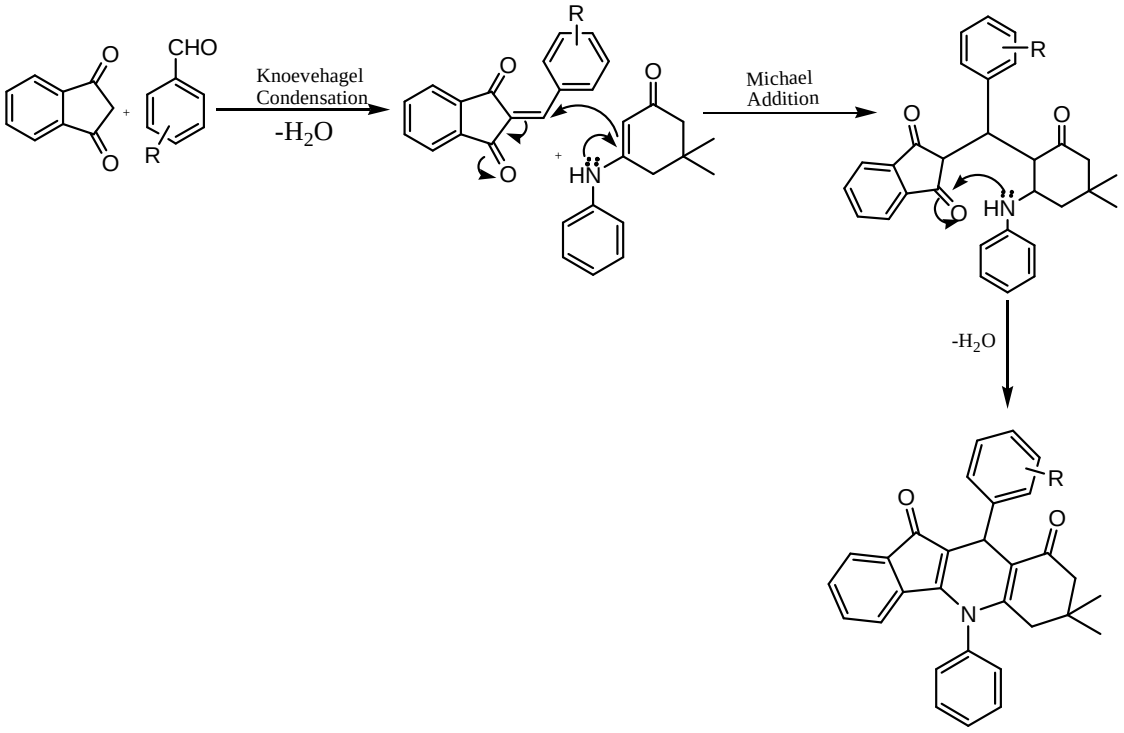
Table No 6. Glide score of series 6 synthesized derivatives (6 a-n)

Entry	R	Product	Glide Score (2VT4)
1	H	6a	-5.531771
2	o-Cl	6b	-5.448951
3	m-Cl	6c	-5.303275
4	p-Cl	6d	-3.924515
5	3,4-Cl_2	6e	-6.887594
6	o-OH	6f	-6.343655
7	p-OH	6g	-5.869209
8	p-OCH_3	6h	-5.725328
9	3-OCH_3-4OH	6i	-5.644422
10	p-NO_2	6j	-5.426378
11	o-NO_2	6k	-5.546985
12	3,4-$(OCH_3)_2$	6l	-5.371902
13	p-$(CH_3)_2NH_2$	6m	-6.591703
14	o-furfuryl	6n	-5.62913
15	Flouxetine	Standard	-7.114571

RESULTS AND DISCUSSION

3.1 Chemistry

Scheme 1 shows a typical synthetic strategy employed to obtain the title compounds (6a-n). A mechanistic rationale exhibiting a probable sequence of events for the indeno-fused heterocycles is given in Scheme 2. The present study proceeds via initial Knoevenagel condensation of 1,3 indanedione (1) with aryl-aldehyde (2a-n) to afford 2-arylideneindene-1,3-dione, which further undergoes *in situ* Michael addition reaction with enaminones (3a) followed by a condensation reaction, leading to cyclisation by the elimination of water to give the final products 6 (a-n). The structures of all the synthesized compounds were established on the basis of spectral analysis. Table no 2 shows the structure, IUPAC name, reaction time, percentage yield and melting point range of series synthesized derivatives (6a-n).



Scheme 2. Plausible mechanism for the synthesis of 5H-indeno[1,2-b]quinoline

The structures of all the synthesized compounds were established on the basis of spectral analysis. The IR spectrum of compound **6a** showed a strong absorption band at 1680 cm^{-1} and 1650 cm^{-1} due to the C=O group, shown in Table No 3. In the ^{1}H NMR spectra two sharp singlet at δ 0.892 and 0.992 ppm corresponds to two methyl groups. A multiplet at δ 2.012-2.267 for 4 CH_2 protons. A sharp singlet at δ 5.111 for 1 CH proton is observed, confirming the completion of cyclization and ring formation. A doublet at δ 5.133-5.152 ppm showing 1 aromatic proton. Aromatic protons (13) were seen in the range δ 6.795-7.649 ppm. Finally elemental analysis authenticates the results. Similarly, a series of 5H-indeno[1,2-b]quinoline-9,11(6H,10H)-dione were prepared using 1,3 indanedione, enaminone with various substituted aryl-aldehyde and finally confirmed with the help of spectroscopic techniques. Moreover the marked hydrogen (shown in a ring in Fig. 3) of the indane part generally appears as a doublet (J=7.6 Hz) at d 5.082-5.100 ppm. This aromatic doublet appears upfield due to the shielding of marked aromatic proton by 5 phenyl ring.

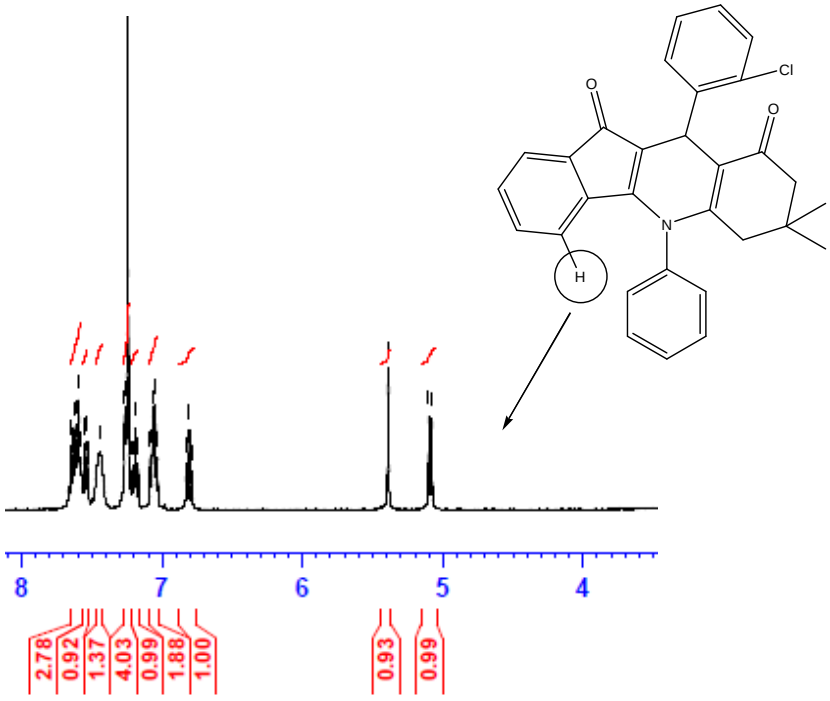


Fig. 3 ^{1}HNMR spectrum of 6b and up field position of the marked aromatic proton

3.2 Pharmacology

In the modern times, anxiety disorders have become common ailments and are usually associated with other psychiatric disorders. Despite the availability of treatment with the arsenal of anxiolytic drugs currently available on the market, many of these pharmaceutical options, such as benzodiazepines, are fairly nonselective and may cause significant adverse effects such as dependence, withdrawal syndrome or muscle relaxation. The obtained data on the antidepressant activity of the compounds and reference drug are given in Table No. 4

The EPM test is a useful and valid animal model for measuring anxiety by investigating aspects of physiological and pharmacological behavior. This method is able to reproduce anxiolytic or anxiogenic effects in rodents in which anxiolytic substances tend to increase the number of entries into the open arms of the device and the time spent there, while anxiogenic substances have the opposite effect. In this study, test compounds increased the number of entries into the open arms of the device and the time spent in the open arms of the maze, behaviors indicative of anxiolytic activity and similar to the positive pattern effects expected following the use of diazepam. The anxiolytic effects of certain drugs such as benzodiazepines are accompanied by decreased locomotor activity and sedation. Development of new anxiolytics that do not induce sedative effects and/or inhibit locomotion would be highly useful. The results of antianxiety activity of compounds 6a-n were shown in table no 4. Derivatives 6a, 6b, 6d and 6k found to be most potent among the series and exhibited significant anxiolytic activity ($^{***}P < 0.001$).

The rotarod test was performed to complement the other experiments and to investigate whether test compounds would cause muscle relaxation in the animals. This test is useful for evaluating the integrity of motor coordination in animals based on their ability to continue walking on a rotating bar for a certain period of time. It can be used to detect physical disabilities due to pharmacological agents such as muscle relaxants and central nervous system depressants. When the performance of animals treated with a certain drug is investigated using the rotating bar and is found to be similar to that of the control group, this suggests that motor coordination has not been impaired in those animals. Test derivatives did not appear to cause muscle relaxation or motor coordination deficit, since there was no decrease in the time spent on the bar compared to the control group.

The neurotoxicities of the synthesized derivatives (6a-n) were determined using the minimal motor impairment-rotarod screen. As shown in Table 5, all compounds did not show any neurotoxic effects at the 40 mg/kg dose administered.

3.3 Docking analysis

3.3.1 Interaction with Serotonin 5-HT_{2A} receptor (2VT4)

In the case of the Serotonin 5-HT_{2A} receptor the synthesized compounds library was docked to the homology model. The inhibitor and standard drug was docked in order to validate the docking model efficiency. The docking simulation of synthesized compounds provides a wide range of docking scores (GlideScore). Standard drug flouxetine has Glide score of -7.114. The docking scores ranged from -6.89 (6e) to -3.92 (6d). Molecules are interacting by good hydrogen bonding with the active site residues of protein. The key amino acid interactions are LEU101, VAL102,TRP117, ASP121, VAL 122, VAL125, CYS199, ASP200, PHE201, TRP303, PHE306, PHE307, PHE325, VAL326, ASN329 and TYR333. Fig. 4 represents the binding orientation of 6e at the binding site surface of the protein (Fig. 4 & 5)

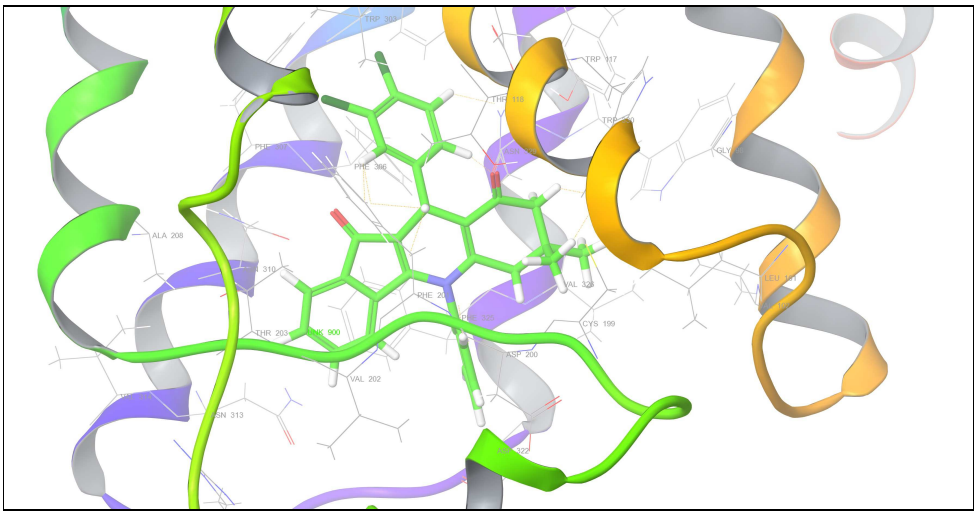


Fig. 4 Docking of 6e with 2VT4

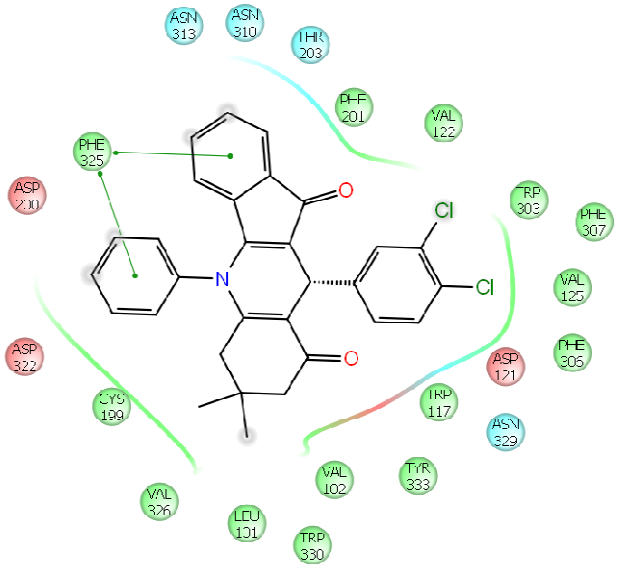


Fig. 5 Two dimension interaction of 6e with 2VT4

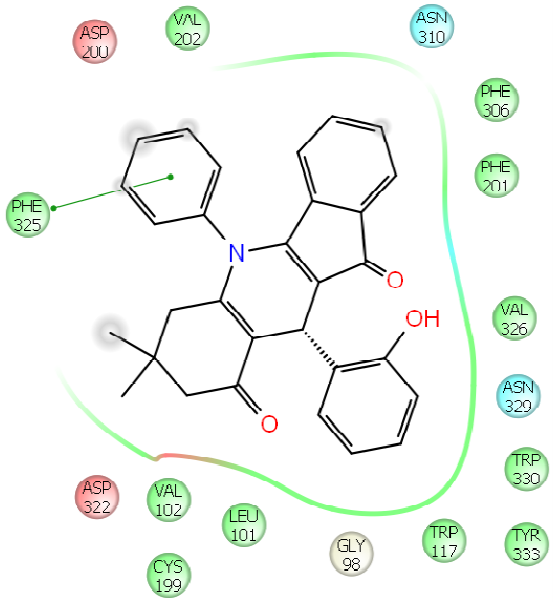


Fig. 6 Two dimension interaction of 6f with 2VT4

CONCLUSION

In summary, we have developed a simple and efficient multicomponent domino synthesis of indeno[1,2-b]quinoline derivatives by the reaction of 1,3-indanedione, aryl-aldehyde, enaminone, and catalyzed by p- toluene sulphonic acid (10 mol%) in ethanol under reflux in good yields. It is worth mentioning that in the course of these reactions. Importantly, this method is suitable for library generation, which makes the methodology more attractive for organic synthesis.

The combined results of this study allow us to conclude that the synthesized derivatives (6a-n) exert an anxiolytic effect on mice without causing motor impairment. Together with other studies conducted in this area, this study may lead to further investigation aimed at discovering new drugs for the treatment of anxiety disorders. The molecular modeling studies also predicted good binding interactions of most active molecules with the Serotonin 5-HT_{2A}

receptor. Therefore, it can be safely concluded that synthesized derivatives (6a-n) would represent a useful model for further investigation in the development of a new class of dual anti-anxiety agents.

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