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MICROWAVE SYNTHESIS AND ANTI-INFLAMMATORY EVALUATION OF SOME NEW IMIDAZOLO QUINOLINE ANALOGS

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ABSTRACT

A Series of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl AZ1-AZ12 substitutes of imidazolo quinoline analogs were synthesized by condensation of substituted imidazole and substituted quinoline.

The title compounds were investigated for anti-inflammatory and its ulecerogenicity activities. All the lead compounds (AZ1-AZ12) were assessed by QSAR and molecular modeling (CADD) studies to predict best physicochemical, pharmacokinetic, toxicological properties and best fit with targets like COX-1 and COX-2. The result indicates that the compounds show convincing activities against inflammation when compared with standard drug (*Ibuprofen).*

Keywords: Imidazolo quinoline, anti-inflammatory, *Ibuprofen.*

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. The synthesis of novel imidazolo quinoline analogs and investigation of their chemical and pharmacological behavior have gained more importance in recents decades for medicinal reasons.[1,2] Substituted imidazolo quinoline analog have been found to have important activities such as anti-inflammatory, antimicrobial and antioxidant.

Microwave technology has been used in inorganic chemistry since 1970s, Giguere and Gedye first implemented it to accelerate the organic reactions in 1986. The slow development of the technique in organic synthesis was principally attributed to the lack of controllability and reproducibility due to using poorly designed domestic microwave ovens as reactors.[3,4] However, with the availability of commercial microwave equipment intended for organic synthesis and the development of the solvent-free techniques, microwave-assisted organic chemistry has experienced exponential growth since the mid-1990s. Microwaves have been employed in organic chemistry to reduce the reaction times from hours to minutes and, to increase yields and selectivity.

EXPERIMENTAL

All chemicals were procured by S.D.Fine Chemicals (India). Melting points of all synthesized compounds were determined in open capillary tubes using Vertigo VMP-1 melting point apparatus and are expressed in c.^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$ as a solvent and TMS as an internal standard. The mass spectra were taken on a Jeol SX-102/PA-6000(EI) spectrometer. C,H,N estimations were done on Carlo Erba 1108(C H N) Elemental Analyser. Domestic Microwave oven was used to synthesize the all title compounds.

7-Hydroxy-4-methyl-2H-chromen-2-one (1)

A solution of resorcinol (0.1 mole) and ethyl acetoacetate (0.1 mole) was mixed with 160 gm of polyphosphoricacid. The reaction mixture was stirred and heated at 75-80 ^oC for 20 mins and then poured

into ice-water. The resultant pale yellow solid mixture was collected by suction filtration, washed with a little cold water and dried at 60°C. Recrystallisation from dilute ethanol yields pure and colorless compound.
(Yield 76%, m.p.187 ^{0}C)
IR (cm^{-1}):3350 (Ar-OH), 3052 (Ar), 1643 (C=O); Anal. Calc'd for $C_{10}H_8O_3$: C, 68.18; H, 4.58; O, 27.25. Found: C, 668.08; H, 4.63; O, 27.30.

7-Acetyloxy / benzoyloxy /benzyloxy-4-methyl-2H-chromen-2-one (2)
4-Methyl-7-hydroxycoumarin (0.1 mole) in acetic anhydride (0.12 mole) and a few drops of pyridine / benzoyl chloride (0.12 mole) in absolute ethanol (10 mL)/ benzyl chloride (0.12 mole) in absolute ethanol (10 mL) was refluxed for 2 hr, and then poured into ice-water. The resultant product was collected by suction filtration, washed with a little cold water and dried at 60°C and recrystallised from absolute ethanol.
[R= $COCH_3$] (Yield 76%, m.p. 176 °C)
IR (cm^{-1}):3050 (Ar), 1645 (C=O), 1510 (Lactone); Anal. Calc'd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62; O, 29.33. Found: C, 66.15; H, 4.47; O, 29.28.
[R= COC_6H_5] (Yield 71%, m.p.172 °C)
IR (cm^{-1}):3050 (Ar), 1645 (C=O), 1510 (Lactone); Anal. Calc'd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32; O, 22.83. Found: C, 72.82; H, 4.31; O, 22.87.
[R= $CH_2C_6H_5$] (Yield 73%, m.p. 181 °C)
IR (cm^{-1}):3050 (Ar), 1645 (C=O), 1510 (Lactone); Anal. Calc'd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30; O, 18.02. Found: C, 76.65; H, 5.37; O, 17.98.

1-(2-Aminoethyl)-7-substituted oxy-4-methylquinolin-2(1H)-one (3)[5, 6]:
Equalent moles of 7-acetyl/ benzoyl / benzyl oxy-4-methyl-2*H*-chromen-2-ones (0.1mole) with diethyl amine (0.1 mole) in glacial acetic acid was refluxed for 6 hr. The excess solvent was then distilled off under reduced pressure and poured into crushed ice (200 gm) to get the solid. The product so obtained was filtered under suction and dried at room temperature. It was purified by recrystalization from absolute ethanol.
[R= $COCH_3$] (Yield 74%, m.p.173°C)
IR (cm^{-1}):3410 (Ar-NH_2), 3054 (Ar), 1652 (C=O); Anal. Calc'd for $C_{14}H_{16}N_2O_3$: C, 64.60;
H, 6.20; N, 10.76; O, 18.44. Found: C, 64.56; H, 6.22; N, 10.74; O, 18.46.
[R= COC_6H_5] (Yield 79%, m.p.179°C)
IR (cm^{-1}): 3410 (Ar-NH_2), 3054 (Ar), 1652 (C=O); Anal. Calc'd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; O, 14.89. Found: C, 70.75; H, 5.62; N, 8.72; O, 14.91.
[R= $CH_2C_6H_5$] (Yield 68%, m.p.172°C)
IR (cm^{-1}): 3410 (Ar-NH_2), 3054 (Ar), 1652 (C=O); Anal. Calc'd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08; O, 10.38. Found: C, 74.05; H, 6.52; N, 9.11; O, 10.32.

Benzoylglycine (4)
Dissolve 0.33 mole of glycine in 250 mL 10% sodium hydroxide solution contained in a conical flask. Add 0.385 mole of benzoic chloride in five portions to the solution. Stopper the vessel and shake vigorously after each addition until all the chloride has reacted. Transfer the solution to a beaker and rinse the conical flask with a little water. Place a few grams of crushed ice in the solution and add concentrated hydrochloride acid slowly and with stirring until the mixture is acid to Congo red paper. Collect the resulting crystalline precipitate of benzoylglycine, which is contaminated with a little benzoic acid, upon a Buchner funnel, wash with cold water and drain well. Place the solid in a beaker with 100ml of carbon tetrachloride, cover the break with a watch glass and boil gently for 10mins (fume cup-board);this extracts any benzoic acid which may be present. Allow the mixture to cool slightly, filter under gentle suction and wash the product on the filter with 10-20 ml of carbon tetrachloride. Recrystallise the dried product from boiling water (about 500mL) with the addition of a little decolourising charcoal if necessary, filter

through a hot-water funnel and allow crystallizing. Collect the benzoylglycine in a buchner funnel and dry it in an oven. The yield is 45gm (76%), m.p. 187°C.
Anal. Calc'd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82; O, 26.79. Found: C, 60.32; H, 5.03; N, 7.85; O, 26.8.

4 - (Substituted benzylidene)-2-phenyloxazol-5-one (5)
Place a mixture of 0.25 mole of redistilled benzaldehyde/4-Cl benzaldehyde/4-OH benzaldehyde/4-OCH_3 benzaldehyde/4-$N(CH_3)_2$ benzaldehyde, 0.24 mole of benzoylglycine, 0.75mole of acetic anhydride and 0.25 mole of anhydrous sodium acetate in a 500 mL conical flask and heat on an electric hotplate with constant shaking. As soon as the mixture has liquefied completely, transfer the flask to a water bath and heat for 2 hr. Then add 100 ml of ethanol slowly to the contents of the flask and allow the mixture to stand overnight. Filter the crystalline product with suction, wash with suction, wash with two 25 ml portions of boiling water: dry at 100°C. The yield of almost pure oxazolone is 40gm (64%) and its melting point 164-165 °C. Recrystallisation from benzene raises the m.p. to 167-168 °C.
[R_1= H] (Yield 79%, m.p.165°C)
IR (cm^{-1}):3416 (Ar-NH_2), 3056 (Ar), 1655 (C=O); Anal. Calc'd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62; O, 12.84. Found: C, 77.5; H, 4.42; N, 5.62; O, 12.46.
[R_1= 4-Cl] (Yield 73%, m.p. 177°C)
IR (cm^{-1}):3416 (Ar-NH_2), 3056 (Ar), 1655 (C=O); Anal. Calc'd for$C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94; O, 11.28. Found: C, 67.75; H, 3.58; Cl, 12.48; N, 4.92; O, 11.27.
[R_1= 4-OH] (Yield 77%, m.p. 182°C)
IR (cm^{-1}):3416 (Ar-NH_2), 3056 (Ar), 1655 (C=O), 3295(OH); Anal. Calc'd for$C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28; O, 18.09. Found: C, 72.45; H, 4.20; N, 5.22; O, 18.13.
R_1= 4-OCH_3] (Yield 78%, m.p.172°C)
IR (cm^{-1}): 3410 (Ar-NH_2), 3054 (Ar), 1652 (C=O), 2896(CH_3); Anal. Calc'd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02; O, 17.19. Found: C, 73.15; H, 4.68; N, 5.09; O, 17.08.
[R_1= 4-N (CH_3)$_2$] (Yield 82%, m.p.198°C)
IR (cm^{-1}): 3416 (Ar-NH_2), 3056 (Ar), 1655 (C=O), 3395(NH); Anal. Calc'd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58; O, 10.95. Found: C, 73.95; H, 5.58; N, 9.59; O, 10.88.
[R_1= 2-OH] (Yield 83%, m.p. 153°C)
IR (cm^{-1}): 3416 (Ar-NH_2), 3056 (Ar), 1655 (C=O), 3295(OH); Anal. Calc'd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28; O, 18.09. Found: C, 72.45; H, 4.46; N, 5.29; O, 17.8.

1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol--1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl substitute
The appropriate 1-(2-aminoethyl)-1, 2-dihydro-4-methyl-2--oxoquinolin-7-yl substitute (0.1 moles) and 4-substituted benzylidene-2-phenyl-oxazol-5-one (0.1 moles) have taken in glacial acetic acid (40 mL) and refluxed for 8 hr. The course of the reaction was monitored every hour with the help of TLC. The excess solvent was then distilled off under reduced pressure and poured into crushed ice to get the solid. The final compounds were filtered, dried and purified by recrystalization from absolute ethanol.

1-(2-((18Z)-4-benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl acetate (AZ1)
(Yield 69 % (0.75 gm), m.p. 148 °C)
M.W.491.5; M.F. $C_{30}H_{25}N_3O_4$; IR (cm^{-1}): 3340 (Ar-NH), 2929(Ar), 1675(C=O), 1528 (CH);
Log P: 3.83; MR: 142.39 [cm^3/mol]; Anal. Calc'd for $C_{30}H_{25}N_3O_4$: C, 73.30; H, 5.13; N, 8.55; O, 13.02. Found: C, 73.28; H, 5.17; N, 8.54; O, 13.01. ^{1}H-NMR: 2.08 CH_3 (-C=O), 3.22 CH_2-CH_2, 7.14-7.30 benzylidene.
MS: 59.0133 ($C_2H_3O_2$): 432.171 ($C_{28}H_{22}N_3O_2$) 230.082 ($C_{13}H_{12}NO_3$): 261.103 ($C_{17}H_{13}N_2O$) 401.138 ($C_{23}H_{19}N_3O_4$): 90.047 (C_7H_6)

1-(2-((18Z)-4-(4-methoxybenzylidene)-4, 5-dihydro-5-oxo--2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl acetate (AZ2)[7, 8]
(Yield 67 % (0.45 gm), m.p. 153^{0}C)
M.W. 521.5; M.F. $C_{31}H_{27}N_3O_5$; IR (KBr) cm^{-1}: 3348 (Ar-NH), 2912(Ar), 1675(C=O), 1520 (CH); Log P: 3.83, MR: 142.39 [cm^3/mol]; Anal. Calc'd for $C_{31}H_{27}N_3O_5$: C, 71.39; H, 5.22; N, 8.06; O, 15.34. Found: C, 71.34; H, 5.28; N, 8.13; O, 15.25. ^{1}H-NMR: 2.08 CH_3 (-C=O), 3.22 CH_2-CH_2, 3.73 CH_3 (methoxy benzylidene)
MS: 59.0133 ($C_2H_3O_2$): 462.182 ($C_{29}H_{24}N_3O_3$): 230.082 ($C_{13}H_{12}NO_3$): 291.113 ($C_{18}H_{15}N_2O_2$)
401.138 ($C_{23}H_{19}N_3O_4$): 120.058 (C_8H_8O)

1-(2-((18Z)-4-(4-(dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-1,2-dihydro-4-methyl-2-oxoquinolin-7-yl acetate (AZ3)
(Yield 72 % (1.0 gm), m.p. 192^{0}C)
M.W. 534.6; M.F. $C_{32}H_{30}N_4O_4$; IR (KBr) cm^{-1}: 3421 (Ar-NH), 2917(Ar), 1646(C=O), 1529(CH), 3390(NH_2); Log P: 3.44; MR: 144.21 [cm^3/mol]; Anal. Calc'd for $C_{32}H_{30}N_4O_4$;: C, 71.89; H, 5.66; N, 10.48; O, 11.97, 15.34. Found: C, 71.84; H, 5.68; N, 10.43; O, 12.05; ^{1}H-NMR: 2.08 CH_3 (-C=O), 3.22 CH_2-CH_2, 2.85 CH_3 (dimethylamine).
MS: 59.0133 ($C_2H_3O_2$): 475.213 ($C_{30}H_{27}N_4O_2$): 230.082 ($C_{13}H_{12}NO_3$): 304.145 ($C_{19}H_{18}N_3O$)
401.138 ($C_{23}H_{19}N_3O_4$): 133.089 ($C_9H_{11}N$)

1-(2-((18Z)-4-(2-hydroxybenzylidene)-4, 5-dihydro-5-oxo--2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl acetate (AZ4)
(Yield 75 % (0.88 gm), m.p. 172^{0}C)
M.W. 507.5; M.F. $C_{30}H_{25}N_3O_5$; IR (KBr) cm^{-1}: 3345 (Ar-NH), 2912(Ar), 1675(C=O), 1525 (CH), 3290(OH); Log P: 3.7; MR: 149.64 [cm^3/mol]; Anal. Calc'd for $C_{30}H_{25}N_3O_5$: C, 70.99; H, 4.96; N, 8.28; O, 15.76. Found: C, 70.98; H, 4.98; N, 8.23; O, 15.81; ^{1}H-NMR: 2.08 CH_3 (-C=O), 3.22 CH_2 -CH_2, 5.0 OH (hydroxybenzylidene)
MS: 59.0133 ($C_2H_3O_2$): 448.166 ($C_{28}H_{22}N_3O_3$): 230.082 ($C_{13}H_{12}NO_3$): 277.028 ($C_{17}H_{13}N_2O_2$)
401.138 ($C_{23}H_{19}N_3O_4$): 106.042 (C_7H_6O)

1-(2-((18Z)-4-benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl benzoate (AZ5)
(Yield 69 % (0.53 gm), m.p. 162^{0}C)
M.W. 553.6; M.F. $C_{35}H_{27}N_3O_4$; IR (KBr) cm^{-1}: 3346 (Ar-NH), 2912(Ar), 1675(C=O), 1525 (CH); Log P: 4.12; MR: 157.57 [cm^3/mol]; Anal. Calc'd for $C_{35}H_{27}N_3O_4$: C, 75.93; H, 4.92; N, 7.59; O, 11.56. Found: C, 75.98; H, 4.95; N, 7.53; O, 11.54. ^{1}H-NMR: 7.41-8.14 Aromatic (benzoate), 7.14-7.30 Aromatic (benzylidene)
MS: 121.029 ($C_7H_5O_2$): 432.171 ($C_{28}H_{22}N_3O_2$): 292.097 ($C_{18}H_{14}NO_3$): 261.103 ($C_{17}H_{13}N_2O$)
463.153 ($C_{28}H_{21}N_3O_4$): 90.047 (C_7H_6)

1-(2-((18Z)-4-(4-chlorobenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl benzoate (AZ6)
(Yield 69 % (0.43 gm), m.p. 192^{0}C)
M.W. 588; M.F. $C_{35}H_{26}ClN_3O_4$; IR (KBr) cm^{-1}: 3442(Ar-NH), 2917(Ar), 1654(C=O), 1588(CH); Log P: 3.44; MR: 144.21 [cm^3/mol]; Anal. Calc'd for $C_{35}H_{26}ClN_3O_4$: C, 71.49; H, 4.46; Cl, 6.03; N, 7.15; O, 10.88. Found: C, 71.48; H, 4.49; Cl; 6.02, N, 7.13; O, 10.88; ^{1}H-NMR: 7.41-8.14 Aromatic (benzoate), 7.22-7.24 Aromatic (chloro benzylidene)
MS: 121.029 ($C_7H_5O_2$): 466.132 ($C_{28}H_{21}ClN_3O_2$):292.097 ($C_{18}H_{14}NO_3$): 295.064 ($C_{17}H_{12}ClN_2O$)
463.153 ($C_{28}H_{21}N_3O_4$): 124.0008 (C_7H_5Cl)

1-(2-((18Z)-4-(4-methoxybenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl benzoate (AZ7)
(Yield 72 % (0.95 gm), m.p. 184^{0}C)
M.W. 583.6; M.F. $C_{36}H_{29}N_3O_5$; IR (KBr) cm^{-1}: 3127(Ar-NH), 2915(Ar), 1678(C=O), 1594(CH), 2890(CH_3); Log P: 5.73; MR: 162.52 [cm^3/mol]; Anal. Calc'd for $C_{36}H_{29}N_3O_5$: C, 74.09; H, 5.01; N, 7.20; O, 13.71. Found: C, 74.08; H, 5.03; N, 7.23; O, 13.66; ^{1}H-NMR: 7.41-8.14 Aromatic (benzoate), 3.73 CH_3 (methoxy benzylidene), 6.72-7.19 Aromatic (methoxy benzylidene)
MS: 121.029 ($C_7H_5O_2$): 462.182 ($C_{29}H_{24}N_3O_3$):292.O97 ($C_{18}H_{14}NO_3$): 291.113 ($C_{18}H_{15}N_2O_2$)
463.153 ($C_{28}H_{21}N_3O_4$): 120.055 (C_8H_8O)

1-(2-((18Z)-4-(4-(dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-1,2-dihydro-4-methyl-2-oxoquinolin-7-yl benzoate (AZ8)
(Yield 74 % (0.8 gm), m.p. 215^{0}C)
M.W. 596.6; M.F. $C_{37}H_{32}N_4O_4$; IR (KBr) cm^{-1}: 3346 (Ar-NH), 2916(Ar), 1675(C=O), 1525(CH), 3395(NH); Log P: 6.29; MR: 167.13 [cm^3/mol]; Anal. Calc'd for $C_{37}H_{32}N_4O_4$: C, 74.48; H, 5.41; N, 9.39; O, 10.731. Found: C, 74.48; H, 5.43; N, 9.37; O, 10.72; 1H-NMR: 7.41-8.14 Aromatic (benzoate), 2.85 CH_3 (dimethylamine), 6.54-7.12 Aromatic (dimethylamino benzylidene)
MS: 121.09 ($C_7H_5O_2$): 475.293 ($C_{30}H_{27}N_4O_2$): 292.097 ($C_{18}H_{14}NO_3$): 304.145 ($C_{19}H_{18}N_3O$)
463.153 ($C_{28}H_{21}N_3O_4$): 133.089 ($C_9H_{11}N$)

1-(2-((18Z)-4-(2-hydroxybenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl benzoate (AZ9)
(Yield 74 % (0.84 gm), m.p. 175^{0}C)
M.W. 569.6; M.F. $C_{35}H_{27}N_3O_5$; IR (KBr) cm^{-1}: 3346 (Ar-NH), 2914(Ar), 1675(C=O), 1525 (CH), 3295(OH); Log P: 5.34; MR: 164.34 [cm^3/mol]; Anal. Calc'd for $C_{35}H_{27}N_3O_5$: C, 73.80; H, 4.78; N, 7.38; O, 14.04. Found: C, 73.88; H, 4.73; N, 7.37; O, 14.02; 1H-NMR: 7.41-8.14 Aromatic (benzoate), 5.0 OH (hydroxy benzylidene), 6.68-7.13 Aromatic (hydroxy benzylidene)
MS: 121.029 ($C_7H_5O_2$): 448.166 ($C_{28}H_{22}N_3O_3$):292.097 ($C_{18}H_{14}NO_3$): 277.098 ($C_{17}H_{13}N_2O_2$)
463.153 ($C_{28}H_{21}N_3O_4$): 106.042 (C_7H_6O)

1-(2-((18Z)-4-benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-7-(benzyloxy)-4-methylquinolin-2(1*H*)-one (AZ10)
(Yield 74 % (0.84 gm), m.p. 175^{0}C)
M.W. 539.6; M.F. $C_{35}H_{29}N_3O_3$; IR (KBr) cm^{-1}: 3346 (Ar-NH), 2914(Ar), 1675(C=O), 1525(CH); Log P: 5.6; MR: 169.77 [cm^3/mol]; Anal. Calc'd for $C_{35}H_{29}N_3O_3$: C, 77.90; H, 5.42; N, 7.79; O, 8.89. Found: C, 77.88; H, 5.43; N, 7.77; O, 8.92; ^{1}H-NMR: 7.19 Aromatic (benzyloxy), 5.20 CH_3 (benzyloxy), 7.14-7.30 Aromatic (benzylidene)
MS: 107.05 (C_7H_7O): 432.171 ($C_{28}H_{22}N_3O_2$):278.118 ($C_{18}H_{16}NO_2$): 261.103 ($C_{17}H_{13}N_2O$)
449.174 ($C_{28}H_{23}N_3O_3$): 90.047 (C_7H_6)

1-(2-((18Z)-4-(4-(dimethylamino) benzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-7-(benzyloxy)-4-methylquinolin-2(1*H*)-one (AZ11)
(Yield 74 % (0.84gm), m.p. 182^{0}C)
M.W. 582.6; M.F. $C_{37}H_{34}N_4O_3$; R_f 0.47; IR (KBr) cm^{-1}: 3346(Ar-NH), 2914(Ar), 1675(C=O), 1525 (CH), 3395(NH); Log P: 6.01; MR: 177.7 [cm^3/mol]; Anal. Calc'd for $C_{37}H_{34}N_4O_3$ C, 76.27; H, 5.88; N, 9.62; O, 8.24. Found: C, 76.28; H, 5.83; N, 9.67; O, 8.22; ^{1}H-NMR: 7.19 Aromatic (benzyloxy), 5.20 CH_3 (benzyloxy), 2.85 CH_3 (dimethylamine), 6.54-7.12 Aromatic (dimethyl amino benzylidene)
MS: 107.05 (C_7H_7O): 475.213 ($C_{30}H_{27}N_4O_2$): 278.118 ($C_{18}H_{16}NO_2$): 304.145 ($C_{19}H_{18}N_3O$)
449.174 ($C_{28}H_{23}N_3O_3$): 133.089 ($C_9H_{11}N$)

1-(2-((18Z)-4-(2-hydroxybenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-7-(benzyloxy)-4-methylquinolin-2(1*H*)-one (AZ12)
(Yield 64 % (0.4 gm), m.p. 151^{0}C)
M.W. 555; M.F. $C_{35}H_{29}N_3O_4$; IR (KBr) cm^{-1}: 3364 (Ar-NH), 2917(Ar), 1666(C=O), 1534(CH), 3081(OH); Log P: 5.34; MR: 164.34 [cm^3/mol]; Anal. Calc'd for $C_{35}H_{29}N_3O_4$ C, 75.66; H, 5.26; N, 7.56; O, 11.52. Found: C, 75.68; H, 5.23; N, 7.57; O, 11.52; 1H-NMR: 7.19 Aromatic (benzyloxy), 5.20 CH_3 (benzyloxy), 5.0 OH (hydroxy benzylidene), 6.68-7.13 Aromatic (hydroxy benzylidene)
MS: 107.05 (C_7H_7O): 448.166 ($C_{28}H_{22}N_3O_3$); 278.118 ($C_{18}H_{16}NO_2$): 277.098 ($C_{17}H_{13}N_2O_2$)
449.174 ($C_{28}H_{23}N_3O_3$): 106.42 (C_7H_6O)

Anti-inflammatory and ulcerogenicity index evaluation
Representative compounds were evaluated for their anti-inflammatory and ulcerogenicity index using carageenan induced rat paw edema and pyloric ligation methods respectively.The percent protection was measured and the activity was compared with standard drug *ibuprofen*.The results of anti-inflammatory screening studies are reported in Table-2.Male albino rats weighing between 100 – 150 gm were used for the experiment.They were divided into various groups. These animals were used for antiinflammatory studies. Thirteen quinazoline derivatives were screened for antiinflammatory activity. The dose levels were fixed based on an acute toxicity studies.

Acute anti-inflammatory model (Carrageenan induced rat hind paw oedema)[9, 10]
The method of Winter.et.al. (Winter.et.al.1963) was used with slight modification. The animals were divided into fifteen groups of six animals each. One group served as a standard (*ibuprofen*) and another group served as control (1% CMC) and rest of the groups were used for the test drugs (AZ1, AZ2, AZ3, AZ4, AZ5, AZ6, AZ7, AZ8, AZ9, AZ10, AZ11, and AZ12). The rats were dosed with test drug orally at 200 mg/kg body weight based on the acute toxicity studies by Miller and Tainter method and standard ibuprofen was also given the same dose level. Test compounds and *ibuprofen* were suspended in 1% CMC which was used as a vehicle for the control group. A solution of 1% carrageenan was used as an inflammatory agent. Food was withdrawn overnight with adequate water before the experiment. The drugs were given orally. After 1 hour, a sub plantar injection of 0.05 mL of 1% carrageenan was administered. The volume of the injected paw was measured at 30 mins, 1hr, 2hr and 3hr intervals with a plethysmograph immediately. The average paw volume in a group of drug treated rats was compared with that of a group with vehicle (control group) and the percentage inhibition of oedema was calculated using the formula.

% Inhibition = (1- Vt / Vc) x 100, Vt = Mean volume of the test drug Vc = Mean volume of the control

The ulcer index was measured and activity was compared with standard drug *aspirin* as per standard procedure.[11, 12]
For estimation of ulcer index, the stomach was cut along the greater curvature and the inner surface was examined for ulcerative with the help of a simple dissecting microscope. Usually circular lesions were observed but sometimes, linear were also seen. The ulcer index was calculated as mentioned below.

Ulcer index=10/X
Where, X=Total mucosal area/Total ulcerated area

RESULTS AND DISCUSSION

The physicochemical properties of the imidazoloquinolines, which were the subject of these biological studies in this report. All the compounds were prepared as shown in scheme 1.2. And 3. The imidazoloquinolines (AZ1-AZ12) made of imidazoline and quinoline through Ethylene Bridge. All the structures were confirmed on the basis of physical and spectral studies viz., IR, ^{1}H-NMR, Mass spectroscopy and elemental analysis.

It allows preparation of many numbers of compounds at the same time in the microwave cavity. Therefore, it is very useful in parallel synthesis and combinatorial synthesis. Moreover, microwave synthesis can lead to improve isolated yields when compared to conventional technology. While it is still at an early stage of development Microwave heating is a very efficient energy source and can be used significantly to reduce reaction, microwave assisted organic synthesis provides an efficient alternative for the synthetic chemist. All the three general schemes (1, 2 & 3) underwent possible microwave irradiation in dry condition by domestic microwave oven.

Anti-inflammatory activity was evaluated by carrageenan induced hind paw oedema tests in rats. The anti-inflammatory activity was observed at intervals of 30 min, 1hr, 2hr and 3hr. The % paw oedema inhibition was found to be high at the 2nd hr of administration and hence the 2nd hr values were discussed with the selected compounds. The anti-inflammatory activity data (Table 4.2.1) indicated the selected test compounds which protected the rats from carrageenan induced inflammation. The compounds AZ1, AZ2, AZ3, AZ4, AZ5, AZ6, AZ7, AZ8, AZ9, AZ10, AZ11, and AZ12 were selected randomly to perform the activity

The ulcer index of the test compounds (AZ1, AZ2, AZ3, AZ4, AZ5, AZ6, AZ7, AZ8, AZ9, AZ10, AZ11, and AZ12). The high ulcer index score for these compounds may be due to the suppression of the prostaglandin synthesis.

The following compounds exhibited prominent activities, the details are as follows:
Anti-inflammatory activity: AZ1, AZ2, AZ3, AZ4, AZ5, AZ6, AZ7, AZ8, AZ9, AZ10, AZ11, AZ12.

CONCLUSION

The microwave method for synthesis of the title compounds offers reduction inreaction times from hours to minutes and, to increase yields and selectivity. All the title compounds were evaluated for an *in vitro* anti-inflammatory activity of by carrageenan paw oedema method. The possible potent anti-inflammatory with less ulcerative effect for the new condensed quinazolines were studied. The data reported in this article may be helpful guide for the medical chemists who are working in this area.

ACKNOWLEDGEMENTS

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Table-1: Characterization of the synthesized compounds

Compound	R	R_1	Mol. formula	Mol. wt	m.pt (^oc)	Solubility	Log P	MR (cm^3/mol)	Anal. Calc'd found
AZ1.	CH_3CO-	H	$C_{30}H_{25}N_3O_4$	491.5	148	$CHCl_3$	3.83	142.39	C, 73.28; H, 5.17; N, 8.54; O, 13.01
AZ2.	CH_3CO-	4-OCH_3	$C_{31}H_{27}N_3O_5$	521.5	150	$CHCl_3$	3.83	142.39	C, 71.34; H, 5.28; N, 8.13; O, 15.25
AZ3.	CH_3CO-	4-$N(CH_3)_2$	$C_{32}H_{30}N_4O_4$	534.6	192	$CHCl_3$	3.44	144.21	C, 71.84; H, 5.68; N, 10.43; O, 12.05
AZ4.	CH_3CO-	2-OH	$C_{30}H_{25}N_3O_5$	507.5	172	$CHCl_3$/CCl_4	3.7	149.64	C, 70.98; H, 4.98; N, 8.23; O, 15.81
AZ5.	C_6H_5CO-	H	$C_{35}H_{27}N_3O_4$	553.6	160	$CHCl_3$/CCl_4	4.12	157.57	C,75.98; H, 4.95; N, 7.53; O, 11.54
AZ6.	C_6H_5CO-	4-Cl	$C_{35}H_{26}N_3O_4Cl$	588	190	$CHCl_3$/CCl_4	3.44	144.21	C, 71.48; H, 4.49; Cl, 6.02; N, 7.13; O, 10.88
AZ7.	C_6H_5CO-	4-OCH_3	$C_{36}H_{29}N_3O_5$	583.6	184	C_2H_5OH	5.73	162.52	C,74.08; H, 5.03; N, 7.23; O, 13.66

AZ8.	C_6H_5CO-	4-$N(CH_3)_2$	$C_{37}H_{32}N_4O_4$	596.6	215	$CHCl_3$	6.29	167.13	C, 74.48; H, 5.43; N, 9.37; O, 10.72
AZ9.	C_6H_5CO-	2-OH	$C35H_{27}N_3O_5$	569.6	175	$CHCl_3/CCl_4$	5.34	164.34	C, 73.88; H,4.73; N, 7.37; O, 14.02
AZ10.	$C_6H_5CH_2$-	H	$C_{35}H_{29}N_3O_3$	539.6	151	$CHCl_3$	5.6	169.77	C, 77.88; H, 5.43; N, 7.77; O, 8.92
AZ11.	$C_6H_5CH_2$-	4-$N(CH_3)_2$	$C_{37}H_{34}N_4O_3$	582.6	182	$CHCl_3$	6.01	177.7	C, 76.28; H, 5.83; N, 9.67; O, 8.22
AZ12.	$C_6H_5CH_2$-	2-OH	$C_{35}H_{29}N_3O_4$	555.6	149	$CHCl_3/CCl_4$	5.34	164.34	C,75.68; H, 5.23; N, 7.57; O, 11.52

% Inhibition = (1- Vt / Vc) x 100, Vt = Mean volume of the test drug Vc = Mean volume of the control

Table-2: Anti-inflammatory *in vitro* activity of compounds AZ1-AZ12

Compound	% Protection			
	30 min	1 h	2 h	3 h
AZ1	35±1.793	47±1.444	49± 1.876	34±1.414
AZ2	39±1.881	49± 1.643	53± 1.372	44± 1.424
AZ3	44±1.079	47± 1.377	52±2.46	43±1.762
AZ4	39±2.198	49± 1.404	57± 1.729	39± 2.306
AZ5	35±1.472	47± 2.174	49±1.752	39± 1.861
AZ6	39±2.66	48±1.872	54±1.4111	41± 1.472
AZ7	39±1.831	42± 1.472	49± 1.876	35± 1.876
AZ8	35±1.333	39±2.357	47±1.875	37±3.246
AZ9	36±1.831	39± 2.412	43± 1.163	32± 1.159
AZ10	27± 1.362	34±1.522	41± 1.476	29± 3.132
AZ11	35±3.214	37±2.327	42± 1.874	36±1.861
AZ12	38± 2.538	41± 1.781	46± 1.323	32± 1.672
STD	46±2.429	53± 2.16	65± 1.871	43±1.871

Significant levels $p < 0.01$ as compared with the respective control
[a] Each value represents the means ± SD (n=6)

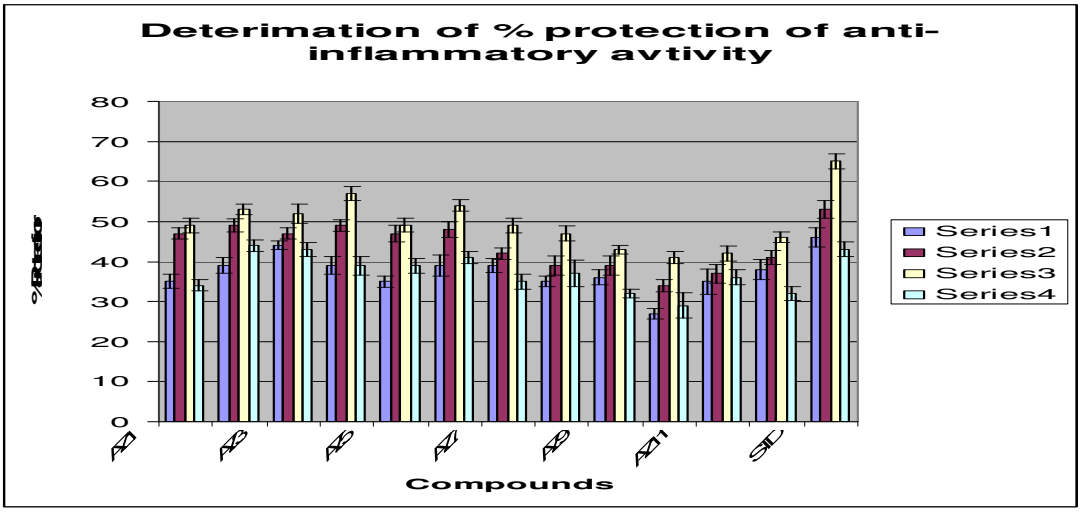


Fig.-1: Percent protection antiinflammatory activity of 1-(2-((18Z)-4-substituted benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl sub

Table-3: Ulcerogenicity index of compounds AZ1-AZ12

Compound	Substituents		Ulcer index
	R	R_1	
AZ1	CH_3CO-	H	0.53± 0.02583
AZ2	CH_3CO-	4-OCH_3	0.54± 0.01891
AZ3	CH_3CO-	4-$N(CH_3)_2$	0.56± 0.2668
AZ4	CH_3CO-	2-OH	0.61±0.01572
AZ5	C_6H_5CO-	H	0.65±0.01452
AZ6	C_6H_5CO-	4-Cl	0.73±0.01881
AZ7	C_6H_5CO-	4-OCH_3	0.71±0.1514
AZ8	C_6H_5CO-	4-$N(CH_3)_2$	0.69±0.02766
AZ9	C_6H_5CO-	2-OH	0.54±0.01671
AZ10	$C_6H_5CH_2$-	H	0.71±0.01862
AZ11	$C_6H_5CH_2$-	4-$N(CH_3)_2$	0.68±0.01651
AZ12	$C_6H_5CH_2$-	2-OH	0.65±0.01572
Control			0.64± 0.01454
Std Asprin			1.7± 0.0216

*Significant levels p <0.01 as compared with the respective control
[a] Each value represents the means ± SD (n=6)

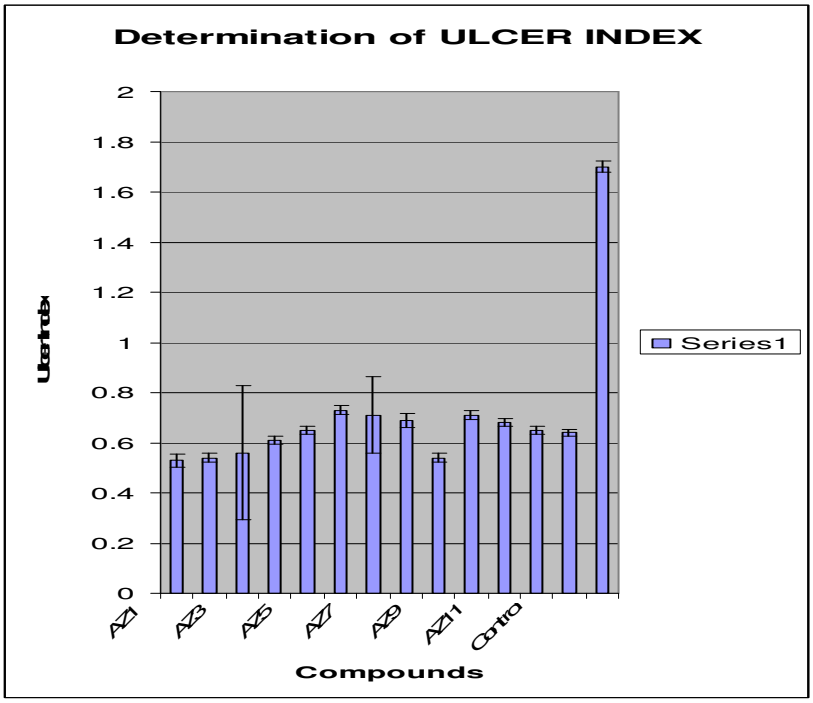
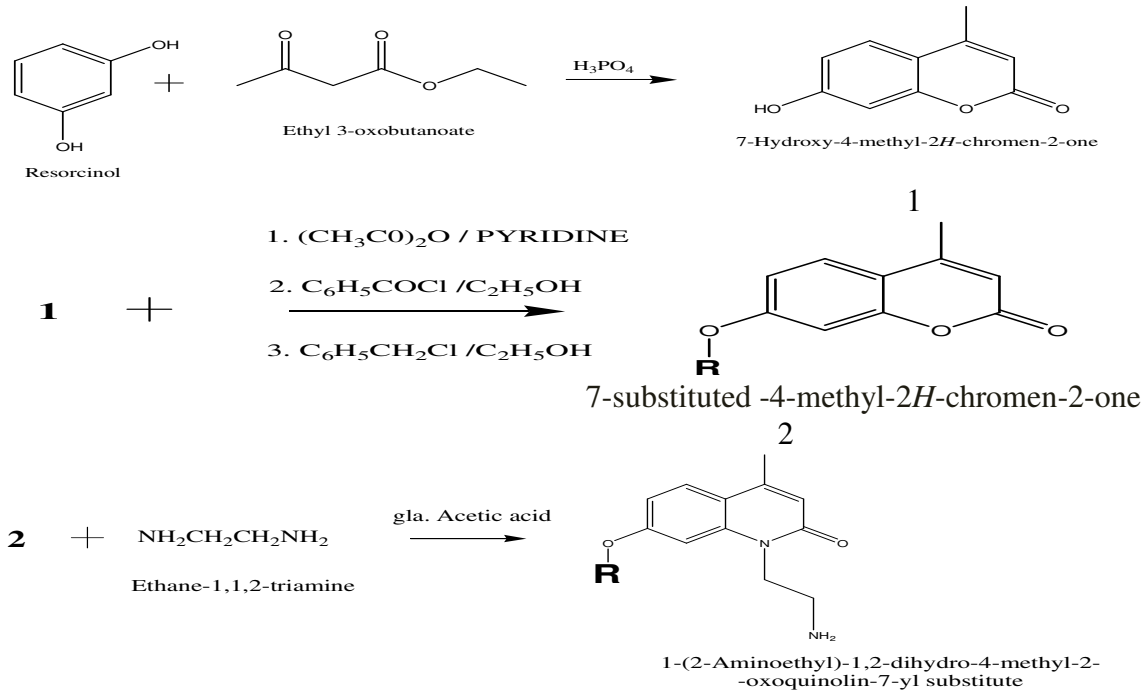


Fig.-2: Ulcerogenicity index of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl sub.



Scheme-1: Synthesis of 7-hydroxy-4-methyl-*2H*-chromen-2-one

Table-4: Substituents on coumarins

S.NO	Substituent (R)
1.	CH_3CO-
2.	C_6H_5CO-
3.	$C_6H_5CH_2$-

Table-5: Substituents on oxazoles

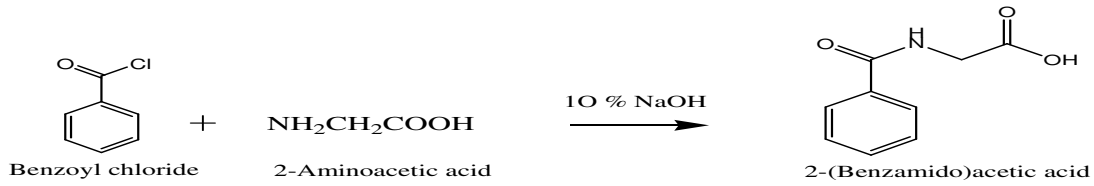
S.No.	R1
1.	H
2.	4-Cl
3.	4-OH
4.	4-OCH3
5.	4-N(CH3)2
6.	2-OH

Table-6: Substituents of imidazolo quinoline derivatives

Compounds	R	R_1
AZ1	CH_3CO-	H
AZ2.	CH_3CO-	4-OCH_3
AZ3	CH_3CO-	4-$N(CH_3)_2$
AZ4	CH_3CO-	2-OH
AZ5	C_6H_5CO-	H

AZ6	C_6H_5CO-	4-Cl
AZ7.	C_6H_5CO-	4-OCH_3
AZ8	C_6H_5CO-	4-$N(CH_3)_2$
AZ9	C_6H_5CO-	2-OH
AZ10	$C_6H_5CH_2$-	H
AZ11	$C_6H_5CH_2$-	4-$N(CH_3)_2$
AZ12	$C_6H_5CH_2$-	2-OH

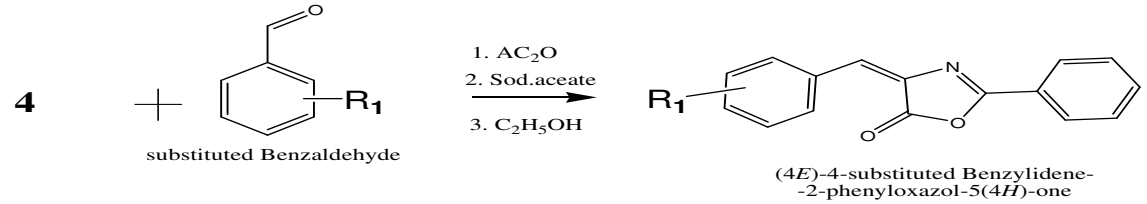
STEP-1: Synthesis of Benzoylglycine



Benzoyl chloride 2-Aminoacetic acid 2-(Benzamido)acetic acid

4

STEP-2: Synthesis of 4-substituted Benzylidene-2-phenyl-oxazol-5-one

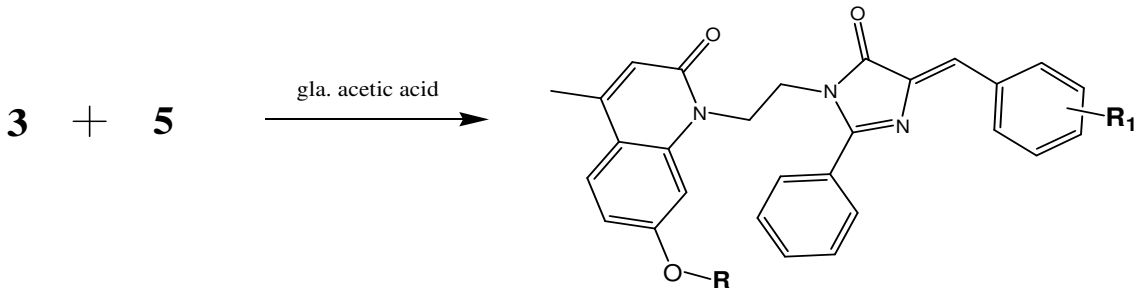


substituted Benzaldehyde

(4*E*)-4-substituted Benzylidene-
-2-phenyloxazol-5(4*H*)-one

5

Scheme-2: Synthesis of 1-(2-Aminoethyl)-1,2-dihydro-4-methyl-2—oxoquinolin-7-yl sub.



1-(2-((18*Z*)-4-substituted benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-
-1-yl)ethyl)-1,2-dihydro-4-methyl-2-oxoquinolin-7-yl substitute

Scheme-3:Synthesis of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol--1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl substitutes

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