SYNTHESIS AND ANALGESIC ACTIVITY OF 2-(4'-SUBSTITUTED PHENYL)-3-[1-(SUBSTITUTED AMINOMETHYL)-2-OXOINDOLIN-3-YLIDENEAMINO] QUINAZOLIN-4-(3*H*)-ONE DERIVATIVES

Gopal Natesan, Choo Shuet Yee, Saravanan Arumugam, Lim Pei Cheng

Department of Medicinal Chemistry, Faculty of Pharmacy, MAHSA University, Kuala Lumpur, Malaysia.

E-mail: gopal@mahsa.edu.my

INTRODUCTION

- ✓ Electron-rich nitrogen heterocyclic plays an important role in diverse biological activities and has been under investigation for a long time because of their important medicinal properties.
- ✓ Among the simple quinazoline derivatives, 2, 3-di substituted quinazoline derivatives possess multiple therapeutic activities.
- ✓ Isatin has wide spectrum of biological activities due to the presence of several reaction centers in the nucleus which allows it to participate in various reactions with different molecules and exhibit similar set of activities such as analgesic, anti-inflammatory, antimicrobial, antibacterial, anticonvulsant and anticancer activities.
- ✓ Incorporating quinazolinone with other important pharmacodynamics heterocyclic nuclei reported to possess potent analgesic activity.
- ✓ Based on the above observations and in continuation of research work in quinazolinone, it was of interest to adjoin the above said moiety to obtain expectedly more potent compounds with lesser side effect.

AIMS AND OBJECTIVES

- ➢ Synthesize and characterize the novel 2-substituted phenyl-3-[1-(substituted amino methyl)-3-oxoindolin-2-ylideneamino] quinazolin-4(3H)-one derivatives.
- ➢ To evaluate the analgesic activity of the synthesized 2,3-disubstituted quinazolin-4(3H)-one derivatives in Swiss albino mice at different doses

MATERIALS AND METHODS

- ⌗ The solvent system used for T L C is Benzene: ethyl acetate (7:3) and visualized the spots either in Iodine chamber or in UV Lamps.
- ⌗ The spectral analysis was done in ^{1}H NMR spectra either on 400 MHz instruments and FT-IR in Shimadzu.
- ⌗ Melting points were determined using Liquid paraffin bath which was uncorrected.

SYNTHESIS

- Synthesis of 2-(4'-substituted phenyl)-benzo-[1,3]-oxazin-4-ones **[I $_{(a-b)}$]**
- Synthesis of 2-(4'-substituted phenyl)-3-amino quinazolin-4-(3*H*)-one derivatives **[II$_{(a-b)}$]**
- Synthesis of 2-(4'-substituted phenyl)-3-[(N-2-oxoindolin-3-ylidene amino)-quinazolin-4(3*H*)-one derivatives **[III$_{(a-b)}$]**
- Synthesis 2-(4'-substituted phenyl)-3-[1-(substituted amino methyl)-2-oxoindolin-3-ylideneamino] quinazolin-4(3*H*)-one derivatives **[IV$_{(a-d)}$]**

PHARMACOLOGICAL ACTIVITY

ANALGESIC ACTIVITY (Acetic Acid Induced Writhing Method)

Animal	Swiss Albino mice (either sex) weight – 20 to 25 gm
Reference Compound	Diclofenac [25 mg/kg body weight (in 0.5% CMC suspension)]
Test Compounds	25, 50 & 100 mg/kg body weight (in 0.5% CMC suspension)
Route of Administration	Intraperitoneal Injection
Method	Writhing was induced in mice by an injection of 0.6% aqueous acetic acid (10 ml/kg body weight). Number of writhing episodes occurring between 5 &15 min after acetic acid injection was recorded

Physical data of 2-(4'-substituted phenyl)-3-[(N-2-oxoindolin-3- ylideneamino) quinazolin-4(3H)-one derivatives (III$_a$ & III$_b$) and 2-(4'-substituted phenyl)-3-[1-(substituted heterocyclic aminomethyl)-2-oxoindolin-3-ylideneamino] quinazolin-4(3*H*)-one derivatives (IV$_{a-d}$)

Code	R	R'	Molecular Formula	% yield	M.Wt	m.p. (°C)	^{1}H NMR Data in DMSO & MASS Spectral Data
III$_a$	H	-	$C_{22}H_{14}N_4O_2$	71	366	246-248	δ 8.25 (b, 1H, -NH), δ 7.73 (m, 1H, H-a, indole), δ 7.07 (d, 1H, H-b, indole), δ 7.3 (m, 1H, H-c, indole), δ 7.80 (m, 1H, H-d, indole), δ 7.33 (m, 3H, H-3', 4', 5'-phenyl), δ 7.64 (t, 2H, H-2', 6', phenyl), δ 7.55 (m, 3H, H-6,7,8, phenyl), δ 7.90 (d, 1H, H-5, phenyl). MS (EI) *m/z* = 367 (M$^+$)
III$_b$	-OCH$_3$	-	$C_{23}H_{16}N_4O_3$	87	396	295-297	δ 3.79 (s, 3H, -CH$_3$), δ 8.2 (b, 1H, -NH), δ 7.58 (m, 1H, H-a, indole), δ 7.07 (d, 1H, H-b, indole), δ 7.34 (m, 1H, H-c, indole), δ 7.65 (m, 1H, H-d, indole),δ 6.90 (d, 2H, H-3', 5', phenyl), δ 7.51m, 2H, H-2',6', phenyl), δ 7.56 (m, 3H, H-6, 7, 8, phenyl), δ 7.9 (d, 1H, H-5, phenyl). MS (EI) *m/z* = 397 (M$^+$)
IV$_a$	H		$C_{27}H_{23}N_5O_3$	65.2	465	226- 228	δ 4.49 (s, 2H, -CH$_2$), δ 2.63 (t, 2H, H-2",6", morpholine), δ 3.69 (t, 2H, H-3",5", morpholine), δ 7.40 (t,2H, H-6, 8, phenyl) δ 7.89 (d, 1H, H-5, phenyl), δ 7.51 (d, 1H, H-7, phenyl), δ 7.63 (m, 1H, H-a, indole), δ 7.07 (d, 1H, H-b, indole), δ 7.24 (m, 1H, H-c, indole),δ 7.79 (m, 1H, H-d,indole), δ 7.19 (m, 3H, H-3',4',5', phenyl), δ 7.51 (t, 2H, H-2',6', phenyl). MS (EI) *m/z* = 466 (M$^+$)
IV$_b$	-OCH$_3$		$C_{28}H_{25}N_5O_4$	77.1	495	219- 221	δ 4.50 (s, 2H, - CH$_2$), δ 3.71 (s, 3H, -OCH$_3$), δ 2.65 (t, 2H, H-2", 6", morpholine), δ 3.70 (t, 2H, H-3", 5", morpholine), δ 6.92 (d, 2H, H-3', 5', phenyl), δ 7.54 (m, 2H, H-2', 6', phenyl), δ 7.64 (m, 1H, H-a, indole), δ 7.07 (d, 1H, H-b, indole) and δ 7.30 (m, 1H, H-c, indole), δ 7.89 (m, 1H, H-d, indole), δ 7.21 (m, 2H, H-6,8, phenyl), δ 7.43 (m, 1 H, H-7, phenyl) δ 8.0 (d, 1H, H-5, phenyl). MS (EI) *m/z* = 496 (M$^+$)
IV$_c$	H		$C_{27}H_{24}N_6O_2$	64	464	206- 208	δ 4.42 (s, 2H, -CH$_2$), δ 2.46 (t, 2H, H-2", 6", piperazine), δ 2.62 (t, 2H, H-3", 5", piperazine), δ 7.64 (m, 1H, H-a, indole), δ 6.90 (d, 1H, H-b, indole), δ 7.31 (m, 1H, H-c, indole) δ 7.73 (m, 1H, H-d, indole), δ 7.37 (m, 3H, H-3', 4', 5', phenyl), δ 7.56 (t, 2H, H-2', 6', phenyl), δ 7.46 (m, 2H, H-6, 8, phenyl), δ7.78 (d, 1H, H-5, phenyl), δ 7.51 (d, 1H, H-7, phenyl). MS (EI) *m/z* = 465 (M$^+$).
IV$_d$	-OCH$_3$		$C_{28}H_{26}N_6O_3$	81.1	494	200- 202	δ 4.42 (s, 2H, -CH$_2$), δ 2.30 (t, 2H, H-2", 6", piperazine), δ 2.46 (t, 2H, H-3", 5", piperazine), δ 7.46 (m, 2H, H-6, 8, phenyl), δ7.79 (d, 1H, H-5, phenyl), δ 7.51 (d, 1H, H-7, phenyl), δ 7.63 (m, 1H, H-a, indole), δ 7.07 (d, 1H, H-b, indole), δ 7.32 (m, 1H, H-c, indole), δ 7.79 (m, 1H, H-d, indole), δ 6.91 (d, 2H, H-3',5', phenyl), δ 7.56 (m, 2H, H-2', 6', phenyl). MS (EI) *m/z* = 495 (M$^+$).

RESULTS AND DISCUSSION

SYNTHESIS

2-(4'-substituted phenyl)-3-[(N-2-oxoindolin-3-ylidene amino)-quinazolin-4(3*H*)-one derivatives **[III$_{(a-b)}$]** and 2-(4'-substituted phenyl)-3-[1-(substituted amino methyl)-2-oxoindolin-3-ylideneamino] quinazolin-4(3*H*)-one derivatives **[IV$_{(a-d)}$]** were synthesized successfully and characterized by Spectral data. (Table 1)

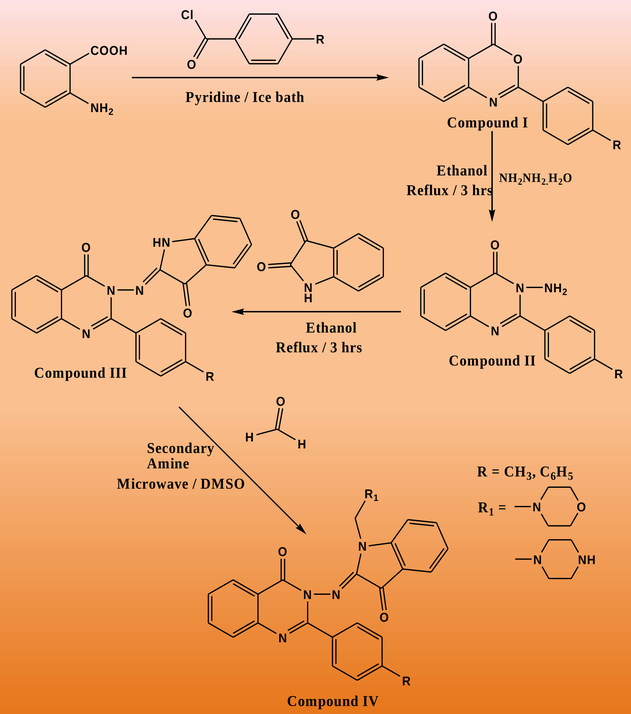
ANALGESIC ACTIVITY

- All compounds showed significant differences when compared with control group ($p<0.001$) which was treated with 0.5% CMC.
- The parent Schiff base derivatives exhibited moderate degree of analgesia and substitution of different amino methyl at nitrogen (N) in the indole pharmacophore of 2-(4'-substituted phenyl)-3-[(N-2-oxoindolin-3-ylidene amino)-quinazolin-4(3H)-one derivatives alters the analgesic activity and final mannich bases exhibited moderate to good degree of analgesia.
- Among the final mannich base synthesized compound IV$_d$, 2-(4'-methoxy phenyl)-3-[1-(piperazinyl methyl)-2-oxoindolin-3-ylideneamino]-quinazolin-4(3H)-one was found to be quite superior in its analgesic activity
- Overall from the results of the analgesic activity of the test compound it has been found that mannich base derivatives (IV$_a$-IV$_d$) were exhibited better analgesic activity than the Schiff base derivatives (III$_a$ & III$_b$) of quinazolin-4(3H)-one nucleus.
- All the Schiff bases and Mannich bases of quinazolinone derivatives showed ceiling effect at 100 mg/kg (bw).

CONCLUSION

- ➢ Novel 2-(4'- substituted phenyl)-3- [(N-2- oxoindolin-3- ylidene amino)-quinazolin- 4(3H)-one derivatives [III (a-b)] and 2-(4'- substituted phenyl)-3- [1-(substituted amino methyl)- 2-oxoindolin- 3-ylideneamino] quinazolin-4(3H)-one derivatives [IV (a-d)] were synthesized and were characterized by proton NMR spectral studies.
- ➢ Analgesic activity of all the test compounds was screened by acetic acid induced writhing method.
- ➢ Parent Schiff bases exhibited moderate degree of analgesia and substitution at N in indole moiety in Quinazolinone Schiff bases alters the analgesic activity.
- ➢ Among the final mannich base synthesized compound IV d , i.e., 2-(4'- methoxy phenyl)-3- [1-(piperazinyl methyl)-2- oxoindolin-3-ylideneamino]- quinazolin-4(3H)- one was found to be quite superior in its analgesic activity.
- ➢ Among the two different secondary amines i.e., morpholine and piperazine used in the synthesis of mannich bases, the piperzine substituted final mannich bases wasfound to be possess better analgesia than morpholine substitution.

SCHEME FOR SYNTHESIS OF QUINAZOLINONE DERIVATIVES

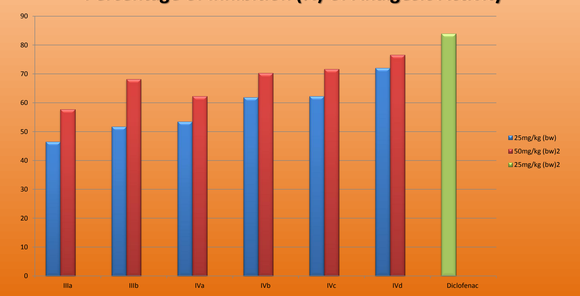


Analgesic activity of Compound (III $_{a-b}$) & Compound (IV $_a$ - IV $_d$) by acetic acid induced writing method at dose of 25 mg/kg (bw) and 50 mg/kg (bw)

No.	Compound code	At dose of 25 mg/kg (bw)		At dose of 50 mg/kg (bw)	
		No. of writing ± SD	Percentage of inhibition (%)	No. of writing ± SD	Percentage of inhibition (%)
1	Control	47.67 ± 1.03	-	47.67 ± 1.03	-
2	IIIa	25.50 ± 1.05	46.5	20.17 ± 0.75	57.69
3	IIIb	23.00 ± 1.26	51.75	15.17 ± 1.17	68.18
4	IVa	22.17 ± 1.17	53.5	18.00 ± 1.10	62.24
5	IVb	18.17 ± 0.75	61.89	14.17 ± 0.75	70.28
6	IVc	18.00 ± 0.89	62.24	13.50 ± 0.84	71.68
7	IVd	13.33 ± 0.82	72.03	11.17 ± 0.75	76.57
8	Diclofenac	7.67 ± 0.52	83.92		

n = 6; One-way ANOVA followed Tukey test

Percentage of inhibition (%) of Analgesic Activity



REFERENCES

- Asif, M. 2014, Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives, International Journal of Medicinal Chemistry 2014: 27.
- Hemalatha, K. and Girija, K. 2011, Synthesis of some novel 2,3-disubstituted quinazolinone derivatives as analgesic & anti-inflammatory agents, Inter Journal of Pharmacy and Pharma Sciences 3(2): 975-1491.
- Rohini, R., Reddy, P.M., Shanker, K., Hu, A. and Ravinder, V. 2010, Antimicrobial study of newly synthesized 6-substituted indolo[1,2-c]quinazolines, European Journal of Medicinal Chemistry 45: 1200-1205.
- Grewal, A.S. 2014, Isatin derivatives with several biological activities, International Journal of Pharmaceutical Research 6(1):1-7.